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WAXY DEGENERATION OF THE DIAPHRAGM

A FACTOR IN CAUSING DEATH IN PNEUMONIA AND
IN OTHER CONDITIONS *

H. GIDEON WELLS, M.D.
CHICAGO

In 1912, Beneke and Steinschneider¹ reported their observation that in guinea-pigs dying of experimental anaphylactic shock, extensive waxy degeneration (Zenker's waxy degeneration) occurred in the skeletal muscles, especially of the diaphragm. Having observed the same changes in a rabbit killed by snake venom, which produces a condition resembling shock in respect to the fall of body temperature, they proposed the hypothesis that the muscle substance contains the "sessile receptors" to which anaphylatoxin and other poisons are bound. They considered the waxy degeneration to be the anatomic expression of such localization of the toxins, and the loss of heat production the physiologic manifestation of injury to the muscle.

This interesting explanation of the observed facts (which I have since observed in guinea-pigs dying of anaphylaxis) is scarcely susceptible of proof, nor tenable in view of the fact that the occurrence of waxy degeneration of the muscles in anaphylaxis is readily explained on entirely different grounds. As was pointed out in the discussion² of the paper of Beneke and Steinschneider, I have found experimental evidence that waxy degeneration of muscles depends on the action of lactic acid produced in the living muscle; whenever this acid accumulates in excess because of overproduction, under-elimination or under-oxidation,³ this condition is present. It was found possible to produce typical waxy degeneration merely by excessive stimulation of voluntary muscle. As lactic acid is normally destroyed in large part by oxidation, it will accumulate in largest amounts under asphyxial conditions, as has often been demonstrated both experimentally and in clinical obser-

* From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

1. Beneke and Steinschneider: *Centralbl. f. allg. Pathol. u. path. Anat.* **23**: 529, 1912.

2. Wells, H. Gideon: *Centralbl. f. allg. Pathol. u. path. Anat.* **23**:945, 1912.

3. Wells, H. Gideon: *J. Exper. Med.* **11**:1, 1909.

vations. Therefore the respiratory muscles, stimulated to maximal contraction in the guinea-pig undergoing asphyxiation from anaphylactic spasm of its bronchi, are in the most favorable possible conditions for the production of maximal quantities of lactic acid.⁴

Human anaphylaxis may produce the same changes. Beneke⁵ observed typical waxy degeneration of the diaphragm in a patient who died of anaphylaxis from puncture of a vein during aspiration of an echinococcus cyst, and old lesions were found in the diaphragm of a patient who had suffered several anaphylactic reactions from the injection of therapeutic serum.

The experiments of Beneke and Steinschneider themselves indicate that anaphylatoxin fixation in the muscles is not necessary for the occurrence of waxy degeneration, for they found that a single lethal dose of peptone injected into the vein of a guinea-pig, killing the animal in a few minutes, may result in waxy degeneration of the diaphragm. As peptone produces death with anaphylactoid phenomena resulting in asphyxia,⁶ the waxy degeneration of the muscles presumably is the result of the asphyxia and the violent compensatory activity of the diaphragm.

As I had previously observed waxy degeneration and rupture of the rectus abdominis in patients with pneumonia, the question arose in my mind as to whether waxy degeneration of the diaphragm might not at times be responsible for death in pneumonia. If guinea-pigs struggling for breath because of bronchial occlusion suffer marked waxy degeneration of the diaphragmatic muscle fibers, patients partially asphyxiated in pneumonia might well suffer a similar fatal injury to their respiratory musculature. The not infrequent occurrence of severe waxy degeneration of the rectus abdominis in pneumonia, even leading to rupture of the muscle, added support to the probability of similar changes in the diaphragm. Therefore I began to collect specimens of diaphragmatic and rectus muscle tissue from patients dying of lobar pneumonia, and found that frequently these muscles showed typical waxy degeneration, often of severe degree. This study was interrupted by the war, but collection of material was begun again later. In the meantime, numerous studies on the pathologic anatomy of influenza

4. Paul (Wien. Arch. f. inn. Med. **7**:531, 1924) attributes to lactic acid the condition of waxy degeneration observed in overworked horses, and in a case of human hemoglobinuria. Hertha (Monatschr. f. prakt. Tierheilk. **32**:165, 1921) describes a similar condition of hemoglobinuria and waxy degeneration in horses fed sugar in 1914-1915 because of shortage of oats, finding an excess of dextro-rotatory lactic acid in the blood, the amount varying with the severity of the condition.

5. Beneke: Beitr. z. Path. Anat. u. z. allg. Pathol. **63**:633, 1917.

6. Hanzlik, P. J.: Basis of Allergic Phenomena, J. A. M. A. **82**:2001 (June 21) 1924.

were published, in some of which attention was called to the frequency and severity of waxy degeneration of the muscles, especially of the diaphragm, in persons dying of this disease.

Sevinthal, Kuczynski and Wolff,⁷ in their elaborate review of the literature on the influenza epidemic of 1918, devote three pages (1088-1091) to the changes observed in the muscles. Most of the authors quoted mention especially changes in the rectus abdominis, but Wegelin, Marchand and Schmord are said to have described waxy degeneration in the diaphragm. The explanation of the occurrence of waxy degeneration of the diaphragm as the result of local accumulation of lactic acid, "nach die Untersuchungen von Wells and Löwit," is accepted by Kuczynski and Wolff, but there is no discussion of a possible responsibility of this waxy degeneration for the fatal outcome in cases of influenza. Reference is made, however, to Ghedini and Fedeli, who found myasthenia and reduction in muscle strength and tonus in influenza.

More recently, articles on related topics have appeared in the American literature. Forbus⁸ reported twenty-five cases of fatal bronchopneumonia which were secondary to influenza or measles, and which showed waxy degeneration in the rectus abdominis. He stated that "In our own cases of pneumonia, consistent search for lesions in other muscles than the recti were fruitless." He did not mention whether the diaphragm was studied, but certainly limitation of the changes to the recti has not been the observation of other students of the muscles in influenza and pneumonia.

Stenström⁹ has reviewed the literature on waxy degeneration of muscles in infectious diseases, calling attention to the fact that both Beneke and Stemmler found the greatest changes in the diaphragm "which is considered to be more disposed toward this degeneration than other muscles on account of its tension and continuous activity." He also cites numerous authors who have described waxy degeneration in influenza as involving particularly the muscles used in respiration. Among them is Utsumi, who found waxy degeneration in nearly every case. Stenström examined the skeletal muscles of forty-seven persons who died from various diseases, and observed some degeneration in every case, the greatest changes usually being found in the diaphragm. He also observed that the temperature of the patient did not seem to have any influence on the intensity of the degeneration. Only a few

7. Sevinthal, Kuczynski and Wolff: *Ergebn. path. Anat. u. Physiol.* **19**:848, 1926.

8. Forbus, W. D.: *Pathologic Changes in Voluntary Muscles*, *Arch. Path. & Lab. Med.* **2**:318 (Sept.) 1926.

9. Stenström, B.: *Degenerative Changes in Skeletal Muscles*, *Arch. Path. & Lab. Med.* **3**:361 (March) 1927.

of his cases, however, were lobar pneumonia, and in these and in the numerous cases of bronchopneumonia, the amount of diaphragmatic involvement does not seem to have been noticeably different from that in other cases. He does not discuss the possible influence of the observed waxy degeneration on the course of the disease.

All the authors cited have overlooked two important early contributions on the subject, which were published in journals of limited circulation. In 1902, Rohrer¹⁰ published an excellent study of the diaphragm in pneumonia and pleurisy. He said: "I wish to call attention to a pathological finding which is, so far as I know, a hitherto undescribed complication. I refer to inflammation of the diaphragm." He described the inflamed diaphragm as thickened and pale, with alternate dark and light areas. This is seen particularly when the lower lobe of the lung is involved and adherent to the diaphragm. Microscopically, the diaphragm may show an acute myositis, with engorged vessels, cellular exudate and hyaline degeneration of the muscle fibers; the perivascular tissue is infiltrated with cells. Leukocytic infiltration is seen especially in cases in which the lower lobe is the seat of pneumonia, but the diaphragm is more or less involved in cases of pneumonia of the upper middle lobe. He describes typical waxy degeneration of the diaphragmatic muscle in these cases, and notes that in most cases in which inflammation is not found, the specimen is taken from a part of the diaphragm remote from the inflamed lung. He says that there is no well defined symptom complex, but that probably the involvement of the diaphragm produces a diaphragmodynia, intensified by coughing, with rapid shallow thoracic respiration. "The inflammatory changes in the diaphragm may be so intense as to cause more or less paralysis of this structure. Paralysis, when it occurs, notably increases the patient's distress and probably not infrequently figures as the immediate cause of death when the demise is sudden. Paralysis of the diaphragm may also result from overexertion as well as from degeneration of the muscle fibers."

Coplin,¹¹ in 1904, presented a paper before the Pathological Society of Philadelphia on "Changes in the Intercostal Muscles and Diaphragm in Infective Processes Involving the Lung and Pleura," citing the paper of Rohrer as the only study known to him of the diaphragm in pneumonia and pleurisy. In a case of lobar pneumonia, Coplin found an acute diaphragmatic myositis, with pneumococci visible in the inflamed areas, and a lymphangitis in the tendinous portion of the diaphragm. In another case of pneumonia changes in the muscle were not seen. In a few cases of pneumococcus pleuritis and of pulmonary and pleural

10. Rohrer: Maryland M.J. 65:391, 1902.

11. Coplin: Proc. Path. Soc. 7:65, 1904.

tuberculosis, waxy degeneration of the intercostal muscle was found with or without myositis. These changes were attributed by Coplin, and also by Rohrer, to spread of bacteria and toxic material from the inflamed pleura through the adjacent muscle tissue by way of the lymphatics. Coplin also discussed at length the probable effect on respiration of this involvement of the muscles of the thoracic wall.

In view of the existence of this abundant literature on the frequency of involvement of the muscles in pneumonia, it is strange that there has been so little consideration of its possible importance. Only Rohrer and Coplin have discussed this, as far as I can find. The clinical treatises on pneumonia do not mention such a possibility, and the muscle pathology of lobar pneumonia is generally neglected. In an analysis of autopsies on 400 cases of pneumonia in the Boston City Hospital, Berry¹² reports that acute myositis of the rectus abdominis was found six times, but he does not say anything concerning the condition of the diaphragm or other muscles of respiration. In their study of the changes in disease of the voluntary muscles, Jewesburg and Topley¹³ do not mention examining the diaphragm; they observed little change in any muscles in acute infections.

My own observations emphasize the frequency of waxy degeneration of the diaphragm and of the rectus abdominis in lobar pneumonia. At least some waxy degeneration is found in nearly every case, varying in degree from swelling and greater or less loss of striation of a few fibers to almost complete disorganization of the muscle, with no normal fibers remaining in the portions of the muscle examined. The details of the process do not require discussion here, as they are not different from the classic changes of Zenker's waxy degeneration, which has been so thoroughly considered by Forbus in his recent articles. Occasionally I have found acute myositis in the diaphragm adjacent to acute diaphragmatic pleuritis, as described by Rohrer, but more often the diaphragm beneath the inflamed pleura has shown only waxy degeneration of varying degree, without actual myositis, although usually the connective tissue is edematous and contains an increased number of mononuclear cells. Generally, there seems to be about as much degeneration of the muscle fibers on the side not involved by the pneumonia; sometimes it may be more marked on this side, which suggests that the muscle on this side may have been working harder than the diaphragm beneath the consolidated lung. Involvement of the rectus muscle is, in my experience, usually less than of the diaphragm, but when either is severely involved the other is usually also much affected.

In persons who survive pneumonia over two weeks, one may find areas of regenerating muscle fibers, indicating that in earlier stages of

12. Berry: *M. Clin. N. Amer.* **4**:571, 1920-1921.

13. Jewesburg and Topley: *J. Path. & Bact.* **17**:432, 1913.

the disease fibers have been ruptured or destroyed without fatal results. In one case in which the patient had severe pneumonia with a temperature varying between 104 and 106 F., with the crisis on the tenth day and death on the twenty-first day, with abscesses of the lungs and acute interstitial nephritis, the number of areas of regenerating muscle fibers in the diaphragm was striking. Some waxy degeneration of the muscle fibers of the diaphragm was still present, and the rectus abdominis showed a severe general waxy degeneration and fragmentation of the muscle fibers, with foci of regeneration.

The main purpose of this paper is to call attention to the great frequency with which the diaphragm, the rectus abdominis, and presumably the other voluntary muscles of respiration, exhibit waxy degeneration in pneumonia, and to indicate the probability that such muscular degeneration may be an important factor in determining respiratory failure in this disease. Unfortunately, the clinical records in most of the cases that I have studied were not sufficiently detailed to make it seem worth while to attempt to correlate the clinical condition and the amount of waxy degeneration of the muscle. While in cases in which the patient's temperature was high and in which there were marked degenerative changes in the liver and kidneys, more degeneration of the muscles generally occurred; in cases of less toxic character, this was not always so. Neither was there a definite relation between the rate of respiration and the amount of waxy degeneration in the material I observed. A study of the entire muscular system in a series of cases of pneumonia, correlated with careful clinical observation, not only on the rate of respiration, but on its character in respect to the relative participation of the thorax, abdomen and diaphragm, the presence or absence of cyanosis, the alkali reserve and other features of the respiratory mechanism, is needed to determine the real importance of the changes in the muscles in respiratory diseases.

SUMMARY

Waxy degeneration of the fibers of the muscles of respiration, especially the diaphragm, is usually present in fatal cases of lobar pneumonia. It is also conspicuous in guinea-pigs that have died of anaphylactic asphyxia, and has been found in fatal cases of human anaphylaxis. Waxy degeneration is known to appear in muscles excessively stimulated and in asphyxiated muscles. Therefore it seems probable that waxy degeneration of the respiratory muscles in pneumonia is, at least in part, the result of overwork and asphyxia of these muscles, and that this degeneration of the muscles may be of importance in the production of respiratory failure in pneumonia and in other diseases requiring severe respiratory effort.

RESISTANCE OF THE LUNG OF THE RABBIT TO TUBERCULOSIS *

RICHARD S. AUSTIN, M.D.

CINCINNATI

Differences between the reactions of animals to infection with the human and with the bovine types of the tubercle bacillus have long been recognized, and the nature of these reactions has frequently been the subject of investigation. Because of the usually decided difference in virulence of the two types of the tubercle bacillus in infection of the rabbit, this animal has often been studied in this connection, with attention most often directed especially to the lesions in the lungs. In fact, a standard method for identifying the type of a recently isolated strain of the tubercle bacillus is based on these typical differences in lesions in the rabbit.

Recently Lewis and Sanderson¹ have reported the results of a study of the histologic expression of the natural resistance of rabbits to infection with human and bovine tubercle bacilli, their conclusions being that "the two types are sharply distinguished by the behaviour of the tubercle bacillus and by the progression of tubercle formation." The quality of the cellular reaction is not different in the two lesions, but the bovine process is progressive, while the tubercles produced by bacilli of the human type finally tend to disappear. It is evident that the bovine bacillus grows more abundantly than the human type in the lung of the rabbit, but the reasons for this are not as yet clearly understood.

In connection with studies on the influence of extracts of normal tissues on the progress of lesions of tuberculosis in rabbits,² it seemed worth while to approach the problem of susceptibility of the rabbit to bovine bacilli from that angle. It had already been found that the essential pathologic differences between the human and bovine types of lesions in the lung of the rabbit are differences of degree and persistence rather than of cellular quality. The fact that occasional animals inoculated with bacilli of the human type developed lesions similar in nature to those produced by bacilli of the bovine type, while, on the other hand, a certain amount of variation was noted in the extent and progress of the lesions caused by this type of bacillus, suggested the possibility that important factors in the determination of the character of the lesions resided in the lung, as well as in the bacilli.

* From the Department of Pathology, University of Cincinnati and Cincinnati General Hospital.

1. Lewis, P. A., and Sanderson, E. S.: *J. Exper. Med.* **45**:291, 1927.

2. Austin, R. S.: *J. Infect. Dis.* **37**:256, 1925.

EXPERIMENTAL METHODS

Rabbits ranging in weight from 1,200 to 1,800 Gm. were the subjects of the studies reported here. Each one received an intravenous injection of from 0.1 to 0.2 mg. (according to weight) of a culture of tubercle bacilli of either the human or the bovine type. The bovine culture possessed well marked virulence for rabbits, while the human culture had always failed to cause the death of rabbits within three months after intravenous injection.

The extract of normal rabbit lung used in these experiments was prepared as described in a previous communication,² except that even greater care was taken to remove as much blood as possible from the organ before cutting it up for saline extraction. The lung was used for the preparation of extracts, because its extract had been found to exert more influence on the lesions of tuberculosis than the extracts of other organs. The sterile saline extract of lung was kept in the icebox and used from one to nine days after preparation. As intravenous injection of such an extract is often followed by the death of the animal, subcutaneous inoculations were made. Even by this route amounts over 0.25 cc. are sometimes not tolerated, and general or local pathologic results follow; therefore, the dose employed was from 0.2 to 0.25 cc. It had previously been found that use of the extract following the injection of bacilli produced more effect on the development of lesions than employment of the extract before such injection; therefore in the experiments here reported, the extract, when used, was inoculated subcutaneously one and eight days after injection of the bacilli.

The rabbits used in these experiments were divided into four groups. All but one animal were subjected to postmortem examination, gross and microscopic.

Group 1.—Rabbits 1 to 6 were injected intravenously with from 0.1 to 0.2 mg. of a culture of human tubercle bacilli. One rabbit was killed 12 days after injection, one 18 days after, and a third 24 days after injection. The other three animals were allowed to live for longer periods, one dying of nontuberculous lesions on the 104th day and another with mixed tuberculous and nontuberculous lesions on the 160th day, while the last rabbit in this group was killed on the 180th day.

Group 2.—Rabbits 7 to 12 were injected intravenously with from 0.1 to 0.2 mg. of a culture of bovine tubercle bacilli. One animal in this group was killed 12 days and another 24 days after injection. The other four animals all died of tuberculosis, with widely distributed lesions, succumbing in turn on the 14th, 17th, 25th and 31st days.

Group 3.—Rabbits 13 to 18 were injected intravenously with from 0.1 to 0.2 mg. of a culture of human tubercle bacilli. Each animal received a subcutaneous inoculation of from 0.2 to 0.25 cc. of sterile saline lung extract 1 day, and again 8 days, after injection of the bacilli. All of these rabbits were killed 12, 18, 24, 73, 120 and 200 days, respectively after injection of the bacilli.

Group 4.—Rabbits 19 to 24 were injected intravenously with 0.1 to 0.2 mg. of a culture of bovine tubercle bacilli. Each animal received a subcutaneous inoculation of from 0.2 to 0.25 cc. of sterile saline lung extract 1 day, and again 8 days, after injection of the bacilli. Three of the animals in this group were killed in turn 12, 18 and 24 days after injection of the bacilli. One of the other three died on the 69th day with widespread active tuberculosis. Of the remaining two animals, one was killed on the 104th day, while the other was still alive and in apparent good health on the 280th day.

The accompanying table presents the more important results of the experiments as far as the lungs are concerned. Extensive and progressing pulmonary lesions were almost invariably accompanied by lesions in other organs, especially in the spleen, liver and kidneys. With the occurrence of lesions in the lungs, associated pathologic changes were regularly encountered in the lymph nodes of the hilum. The degree of involvement of the lungs is in general a fair indication of the degree of susceptibility of the rabbit to infection with tubercle bacilli injected intravenously. Furthermore, the number, size and nature of the tubercles in the framework of the lung bear a relation to the severity of

Results of Experiments in Lungs

Rabbits	Type of Tubercle Bacilli	Lung Extract Used	Days Before Death	Died or Killed	Tubercle Formation in the Lungs
1	Human	No	12	K	Small, discrete, non-necrotic
2	Human	No	18	K	Small, discrete, non-necrotic
3	Human	No	24	K	Small, discrete, occasional necrotic centers
4	Human	No	104	D	Few, small, largely fibrotic
5	Human	No	100	D	Few, some conglomerate and caseous
6	Human	No	180	K	Very few, but two large, caseous and fibrotic
7	Bovine	No	12	K	Small, numerous, discrete, occasional necrotic centers
8	Bovine	No	14	D	Larger, more numerous, conglomerate, frequent necrotic centers
9	Bovine	No	17	D	Like no. 8
10	Bovine	No	24	K	Like no. 8, with more necrosis and irregularity
11	Bovine	No	25	D	Like no. 10, with more irregularity
12	Bovine	No	31	D	Like no. 11, with more necrosis
13	Human	Yes	12	K	Very small, discrete, non-necrotic
14	Human	Yes	18	K	Very small, discrete, non-necrotic
15	Human	Yes	24	K	Small, discrete, non-necrotic
16	Human	Yes	73	K	No lesions
17	Human	Yes	120	K	Few, mostly small; some caseous and fibrotic
18	Human	Yes	200	K	No lesions
19	Bovine	Yes	12	K	Very small, discrete, non-necrotic
20	Bovine	Yes	18	K	Small, discrete, non-necrotic
21	Bovine	Yes	24	K	Small, discrete; occasional necrotic centers
22	Bovine	Yes	60	D	Few, but large, conglomerate, irregular and necrotic
23	Bovine	Yes	104	K	Few, large, conglomerate, caseous, but fibrotic
24	Bovine	Yes	(Rabbit living 280 days after injection)

the disease; so tubercle formation has been used in the table as an indication of the relative susceptibility or immunity of the animals to infection. Exudative reaction in the air spaces of the lungs in these groups of animals is relatively inconspicuous. Diffuse, or nontubercular, infiltration of the framework of the lung is more prominent than tubercle formation in earlier stages of the disease; the latter condition, in its various stages of development, is the outstanding lesion in rabbits examined at the periods after injection shown in the table.

EXPERIMENTS WITH RECOVERED BACILLI

In order to learn whether the use of lung extract had any persisting effect on the tubercle bacilli, cultures were made from the lesions of rabbits 15, 17, 21 and 23. The cultures from rabbit 17 yielded no growths, but those from rabbit 15 gave growths of tubercle bacilli which produced lesions correspond-

ing to those in the animals of group 1. In a similar way the bacilli recovered by culture from rabbits 21 and 23 caused lesions comparable to those in the rabbits of group 2. Evidently the injection of lung extract does not produce a persisting change in the characteristics of the bacilli.

COMMENT

The first two groups of animals shown in the table, rabbits 1 to 6 and 7 to 12, present the differences in the matter of tubercle formation in the lungs which result from intravenous injections of human and bovine types of tubercle bacilli. They also show the contrast between the lengths of time animals survive after injection with the two types of bacilli, the bovine type being quickly fatal, while the human variety permits much more extended existence. The particular strain of the human type of the tubercle bacillus which was used in these experiments, while undoubtedly of the human type, has not infrequently contributed to the death of rabbits some months after it has been injected intravenously in doses of from 0.1 to 0.2 Gm. A probable example of this may be noted in the case of rabbit 5.

Comparison of the untreated group of animals injected with the human type of bacilli with the group receiving the same kind of bacilli, but subsequently being inoculated with lung extract, brings out the apparent influence of lung extract in retarding the development of lesions in the lungs. A similar comparison of the two groups of the bovine type, untreated and treated, reveals an even more striking contrast, and in addition shows evidence of prolongation of life because of the inoculation of the lung extract. In regard to tubercle formation in the lungs and in connection with the length of life after injection of bacilli, it would appear that the action of the lung extract had changed the relationship between the bovine bacilli and the lungs to one closely resembling that characteristically existing between bacilli of the human type and the lungs. The essential cause for this changed relationship is not to be found in the bacilli, since they still possess their usual virulence for rabbits when removed from the treated animals and injected into untreated rabbits; so the cause is presumably in the lungs. The protective substance indicated by these experiments is probably not derived from the fluid or cellular elements of the blood. There remain several possibilities in connection with the fixed cells of different varieties in the framework of the lung, one of the most interesting types being the endothelial cells of the vessels. A number of investigators believe that from these cells are derived many of the large mononuclear phagocytes associated with the lesions of tuberculosis. The stimulation to activity on the part of these or of other varieties of cells of the lung in the production of protective substances may possibly be the way in which the inoculation of lung extract produces increased resistance.

It is not clear whether the inoculated extract by itself increases the resistance of the animal or whether the extract stimulates the increase of substances already present in the lung or elsewhere, but in too small amounts successfully to combat the bovine type of bacilli under usual conditions. The latter possibility would seem the more likely, particularly in view of the fact that rather small amounts of extract were used, and that only two inoculations were made.

In the table it will be noted that all the treated rabbits do not present lesions contrasting sharply with the lesions in the untreated animals. This may be due to the fact that the lung extract is not "standardized," different samples probably varying somewhat in protective potency. However, the very unevenness of the results presented in the table might be employed to support the contention that the difference in resistance of the rabbit to infection with tubercle bacilli of the human and of the bovine type is due to the existence of a quantitative element in the situation. In other words, more of the same substances which discourage the growth of bacilli of the human type will also interfere with the multiplication of bacilli of the bovine type. This interpretation of these experiments lends support to the conclusion of Lewis and Sanderson¹ to the effect that it is more likely that failure of the bacilli to multiply may be due to some positive growth-restraining factor rather than to a failure of suitable nutritive materials. In the experiments here reported, no careful check was made of the numbers of bacilli in lesions of different stages of development, but from the work of Lewis and Sanderson,¹ it is evident that abundant growth of bacilli (bovine type) is accompanied by progressing and destructive lesions.

CONCLUSIONS

Rabbits inoculated subcutaneously with a sterile saline extract of rabbit lung after being injected intravenously with tubercle bacilli usually develop lesions in the lung of less extent than do rabbits not receiving the lung extract. The differences are more striking in animals injected with the bovine type of bacilli than with bacilli of the human type. Furthermore, in infection with the bovine type of bacilli, the duration of life is decidedly lengthened by inoculation of extract, and the lesions in the lung develop in a way more or less characteristic of those ordinarily produced by infection with the human type of bacilli. It is possible that the same unknown defensive substances are employed to combat infections of both the human and the bovine type, but a larger amount of such substances is necessary in dealing with the bovine type of bacilli. In other words, the difference in the resistance of the rabbit lung to the two types of infection may be largely due to a quantitative difference in the defensive factors that are needed.

THE SO-CALLED SMALL ROUND CELL INFILTRATIONS

I. POLIO-ENCEPHALITIS AND ACUTE EPIDEMIC ENCEPHALITIS *

N. A. MICHELS, Sc.D.

AND

J. H. GLOBUS, M.D.

Assistant Professor of Neuro-Anatomy and Neuropathology,
New York University Medical School

NEW YORK

The problem as to the histogenous or hematogenous origin of the various types of cells that appear in perivascular infiltrations and in other inflammatory reactions has in recent years received renewed investigation and discussion. Despite the variety of new methods employed (intra vitam staining, injection of colloidal dyes and India ink suspensions, growth of various tissues in vitro) under conditions of inflammation normally or artificially produced, unanimity of opinion as to the genesis of these cells is still lacking.

For all practical purposes the problem is no further elucidated than in the time of Cohnheim and Virchow. As early as 1867 the former proved conclusively that white corpuscles (polymorphonuclears) emigrate from the blood stream, thereby rendering untenable the then prevalent Virchow theory of the exclusive origin of these cells from fixed connective tissue cells.

The investigations and conclusions arrived at since then are far too many and divergent to be detailed here. An excellent review of the work accomplished in this field has recently been given by Foot in his studies on endothelial reactions.¹

For purposes of orientation, however, the conflicting opinions may be summarized and grouped under the following headings:

a. Those maintaining an exclusive hematogenous origin of the cells: Baumgarten,² Metchnikoff, Schridde and, partly, McJunkin.³

*From the Department of Neuro-Anatomy, New York University and Bellevue Hospital Medical School and the Department of Neuropathology, Mt. Sinai Hospital.

*The work was aided by a grant from the Emanuel Libman Fellowship fund.

1. Foot, Nathan Chandler: The Endothelial Phagocyte. A Critical Review, *Anat. Rec.* **30**:15, 1925.

2. Baumgarten: Ueber die Herkunft der in Entzündungsherden auftretenden Lymphkoerperchenartige Elemente, *Centralbl. f. allg. Pathol. u. path. Anat.* **1**:764, 1890.

3. McJunkin, Frank Adam: The Origin of the Phagocyte Mononuclear Cells of the Peripheral Blood, *Am. J. Anat.* **25**:27, 1919.

- b. Those advocating an exclusive histogenous origin from pre-existent connective tissue cells: Ribbert,⁴ Dominici,⁵ Foa, Marchand,⁶ Herzog⁷ and Ferrata and Papenheim, the last mentioned two denying emigration of lymphocytes.
- c. Those holding a middle position, proposing a mixed origin: Maximow.⁸
- d. Those claiming the problem insoluble: Forbes and Marcora,⁹ and, finally,
- e. Those favoring a predominant, if not an exclusive, production of the cells by vascular endothelium: Mallory,¹⁰ and notably Foot.¹¹

In current contributions, discussion centers about the position taken by Foot and Maximow. The latter advanced his theory of a mixed origin as early as 1902, in studies of experimental aseptic inflammation, and has consistently held the same opinion in his works on purulent inflammation, on the ontogenesis of blood cells, on the nature of connective tissues and, recently, on the cultures of lymphoid tissues, both normal and inoculated with tubercle bacilli.

Briefly stated, Maximow's three sources for the cells appearing in inflammation are: (a) partly from pre-existing, round wandering cells (emigrated lymphocytes); (b) partly from clasmatocytes and small, clasmatocyte-like adventitial cells of vessels, and (c) the vast majority from the blood vessels through emigration.

The emigrated hemic lymphocytes (small, medium and large) undergoing hypertrophy were termed by Maximow "polyblasts," "because they

4. Ribbert: Beitrage zur Entzündung, Virchows Arch. f. path. Anat. **150**: 391, 1897.

5. Dominici: Polynucleaire et macrophages, Arch. de méd. expér. et d'anat. path. **14**:9, section 1, 1892.

6. Marchand: Ueber die Herkunft der Lymphocyten und ihres Schicksals bei der Entzündung, Verhandl. der deutsch. path. Gesellsch., 1903.

7. Herzog, G.: Experimentelle Untersuchungen über die Einteilung von Fremdkörpern, Beitr. z. path. Anat. u. z. allg. Pathol. **61**:377, 1915; Ueber Capillarendothelien als Wanderzellen, Klin. Wchnschr. **13**:535, 1924.

8. Maximow: Experimentelle Untersuchungen ueber die Entzündliche Neubildung con Bindegewebe, Beitr. z. path. Anat. u. z. allg. Pathol., Supp. 5, 1902, vol. 32; Untersuchungen ueber Blut und Bindegewebe, Arch. f. mic. anat., 1909, vol. 73; 1910-1911, vol. 76; 1922, vol. 96; Tuberculosis in Mammalian Tissue in Vitro, J. Infect. Dis. **34**:549, 1924.

9. Marcora: Haematologica **11**:323, 1921.

10. Mallory: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914.

11. Foot, N. C.: The Macrophages of the Loose Connective Tissue, J. M. Research **40**:353, 1919; The Endothelium in Experimental General Miliary Tuberculosis, J. Exper. Med. **33**:271, 1921; The Endothelium in the Healing of Aseptic Wounds in the Omentum of Rabbits, *ibid.* **34**:635, 1921; The Endothelial Response in Experimental Tuberculous Meningoencephalitis, *ibid.* **36**:607, 1922; Changes in the Distribution of Colloidal Carbon Noted in the Lungs of Rabbits Following Splenectomy, *ibid.* **37**:139, 1923; Changes in the Distribution of Tubercle Bacilli and Tubercles in the Organs of Rabbits Following Splenectomy, *ibid.* **38**:263, 1923.

displayed an amazing variety of prospective potencies and produced many other cell types found in the inflammation area."

Admitting, with others, polyvalent hemohistiopoietic powers on the part of the reticulo-endothelial apparatus, Maximow for nearly twenty-five years has consistently refused to admit similar powers in the general vascular endothelium. The latter, while hematopoietic in the first blood-forming organs and in the early embryogenesis, never gives rise to ameboid wandering cells in the later periods of intra-uterine or in adult life, not even in inflammatory conditions. Its specific character is clearly demonstrable in lymphoid tissue culture (normal or inoculated with tubercle bacilli), in which "the endothelial cells either keep their former arrangement in tubes and produce sprouting capillaries, or they become transformed into strands of common fibroblasts" (Maximow). Even the latter are irrevocably established elements, never producing polyblasts or being transformed into epithelioid cells.

With regard to inflammation, Maximow⁸ categorically stated:

Contrary to the dominant opinion, I never could find in my studies on inflammation any proof for the assumed transformation of ordinary endothelial cells of the blood or lymph vessels into wandering phagocytic cells, i. e. into polyblasts.

Of decided interest and a sufficient cause for renewed discussion is the position taken by Foot in holding the general vascular endothelium responsible for the production of the majority of the free cells appearing under inflammatory conditions.

In a recent series of papers, Foot¹¹ maintained that a colloidal carbon suspension (India ink) injected intravenously acts as a specific indicator of the cells derived from the vascular endothelium, notably that of the capillaries. His contention was based on the fact that forty-five minutes after the injection, carbon is found stored in the endothelium (Kupffer cells) of the liver, lung and bone marrow and is also found free in the splenic sinuses or stored in their endothelium. The last, while morphologically different from the reticulo-endothelium, is nevertheless of equal importance functionally in respect to the formation of both phagocytes and reticulin fibers.

Proceeding with his newly found "specific endothelial agent" (engulfed carbon particles), Foot maintains that aside from the epithelium of the liver (into which carbon may be forced after repeated injections), the carbon granules are taken up only by cells derived from the capillary endothelium. Since, therefore, macrophages, polyblasts, clasmotocytes, large and small mononuclears, resting wandering cells, histiocytes, epithelioid cells, syncytial and giant cells take up carbon in variously produced experimental lesions, the term "endothelial phagocyte" is resuscitated as the common designator for the "majority of these

cells." The term, in his opinion, is justifiable, for "endothelial" means that they are derived from the nearby vascular endothelium and "phagocyte" indicates their function. In addition, they may produce connective tissue, collagen fibers and new vessels.

A hematogenous origin of these cells from emigrated lymphocytes with subsequent differentiation in the tissues (Maximow's polyblasts) is denied by Foot. Like Metchnikoff, however, he admits that some of them represent emigrated mononuclears; these in his opinion were not brought to the site of the inflammation by the blood stream from distant hematopoietic organs, but represent intravascular desquamation products of the nearby capillary endothelium. Finally, a minority of the cells represent migratory individual cells coming from neighboring areas of areolar tissue. Summarizing, Foot says:

Probably the entire endothelium considered in the freest sense of the term presents a persisting mesenchymal, embryonoid tissue capable of extensive differentiation or dedifferentiation, without which the body would be incapable of repairing the ravages of injury and disease.

In view of the foregoing investigations, the problem as to the origin of the large number of free cells appearing in perivascular infiltrations, such as occur in poliomyelitis and encephalitis, suggested itself to us. While various investigators in the past have recorded their observations in this regard, much remains to be said about the exact formative process of such infiltrations.

Von Economo,¹² in his comprehensive monograph, while admitting a hematogenous origin for most of the cells, by no means minimized the active rôle played by the adventitial cells in the production of polyblasts and plasma cells.

That these cells are of mixed origin was likewise suggested by Dionisi,¹³ with this difference, that while a small percentage comes from the blood stream, the majority are derivatives of histiocytes, themselves differentiation products of pre-existing connective tissue elements.

Guizzetti,¹⁴ reporting a case of encephalitis, advocated an exclusive origin of the cells from the blood stream.

Recently, Marcora⁹ studied five cases of acute epidemic encephalitis. In enumerating the cell types encountered, he mentions: lymphocytes, polyblasts, clasmatoocytes, plasma cells, pigmented macrophages and occasional granulocytes. In vessels in which the infiltration has reached considerable proportion, it is impossible, in his opinion, to determine whether the constituent cells originated from the blood stream, local tissue or from both. Studying vessels with initial infiltration, however,

12. Von Economo, G.: *L'Encephalite Letargica*, Policlinico (sez. med.) 27:193, 1920.

13. Dionisi, D.: *Sull'Encephalite Letargica*, Riv. Sanit. Siciliana, 1920, no. 5.

14. Guizzetti: *Per l'anatomic patologica dell'encefalite letargica*, *Reforma Medica*, 1920, no. 36.

he observed a notable contribution from the adventitial cells. These divide mitotically and frequently differentiate into typical plasma cells, a process visible in the fusiform cells by the fact that their cytoplasm becomes granular and deeply basophilic.

Marcora claimed that the hemic origin of the cells is insufficiently supported, since it is based only on the radial seriation of lymphoid cells around blood vessels and not on actual observation of a process of emigration of lymphocytes. He also pointed out that superimposed elements or oblique sections of cells might erroneously be taken as emigrating cells. He thus regarded diapedesis of the infiltrating elements as not proved and concluded that the infiltration cells must be considered as histogenous in origin, viz., products of the perivascular adventitial cells which have undergone proliferation and transformation.

MATERIAL AND METHODS

We have thought that inflammatory lesions in the central nervous system offer a peculiarly favorable opportunity for the study and the possible determination of the source of origin of the cells in the so-called perivascular infiltrations. There is a strong tendency for the inflammatory elements to be restricted to the so-called adventitial spaces for relatively long periods, undergoing various morphologic changes. Under such conditions, the cells can be studied with fair accuracy, and light can be thrown on their ultimate origin.

The material of twelve cases is included in this study. Seven of these may be regarded anatomically as forms of polio-encephalomyelitis, though clinically only three were designated as such, while four of the group were diagnosed as polio-encephalitis and one as acute epidemic encephalitis.

The remaining four cases of the entire group studied include types of clinically diagnosed and anatomically verified cases of acute epidemic encephalitis. The variations occurring in this subgroup will be discussed along with the anatomic descriptions.

Numerous blocks of tissue were taken from many and various regions, including the cerebrum, basal ganglions, midbrain cerebellum, pons, medulla and spinal cord.

The material was fixed in formalin and Zenker's fluid, embedded in paraffin and sectioned at an average of 5 microns. The staining method generally used was that of Maximow, viz., hematoxylin followed by the azure-eosin combination. In specific instances other methods, such as Weigert's for elastic tissues and Mallory's for connective tissue, were used.

There appears to be fairly convincing evidence that the cellular elements in the so-called perivascular round cell infiltration that occurs in inflammatory lesions of the central nervous system are modified forms

of lymphocytes (small or large) and mononuclear leukocytes, which have emigrated by diapedesis from the blood stream into the adventitial spaces.¹⁵

In these spaces the cell-emigrants undergo changes in form and size and give rise to various cellular forms. While these cells remain confined for a variable length of time to the Virchow-Robbin (adventitial) space, they frequently continue their movement (migration) into the tissue adjoining the vessels, which we shall for convenience of description designate as "extravascular territory," constituting the so-called "focal areas of infiltration."

In the table appended to this article we have assembled such of our observations as lend themselves to numerical or graphic presentation for purposes of rapid orientation and to serve as an index of the observations described in greater detail under various headings in the body of the paper.

REPORT OF CASES

POLIO-ENCEPHALOMYELITIS

CASE 1.—*History.*¹⁶—R. M., a boy, aged 4, admitted to the hospital on Oct. 30, 1920, had suddenly developed headache and a rise in temperature two days before. Soon afterward his eyes became crossed, he became drowsy and vomited several times.

The patient was acutely ill. Facial paralysis and left internal strabismus were present. The pupils were contracted, the neck was rigid and bilateral Babinski sign was present. The knee jerks were active and unequal, the left greater than the right. The spinal fluid was bloody. Respiration was irregular. The patient failed rapidly, dying on the day following admission. The clinical diagnosis was acute epidemic encephalitis or polio-encephalitis; the anatomic diagnosis, acute polio-encephalomyelitis.

Microscopic Examination.—Adventitial Infiltrations: As seen from figure 1, sections of the brain were characterized by pronounced perivascular and widespread focal infiltrations with many migrating lymphoid cells, the nature of which will be described later. In extent, the perivascular infiltration averaged four or five rows of lymphoid cells, the capillaries showing a minimum of from eight to fifteen rows.

15. It is highly gratifying that since the completion of this work an important contribution on this subject has been made by Eliot (Eliot, Calesta: *The Origin of the Phagocytic Cells in the Rabbit*, Bull. Johns Hopkins Hosp. **39**:149, 1926), who by an experiment, ingenious although remarkable in its simplicity, came to conclusions directly opposite to those drawn by Foot from his experiments. By means of intravenous injection of white blood cells into rabbits into which carmine particles have previously been injected, Eliot was able to follow the transformation of white blood cells into the various forms of the phagocytic cell, constituting the so-called reticulo-endothelial system, which in the light of the experiment are regarded by the author as modified extravasated white blood cells (*The Reticulo-Endothelial System and the Origin of Phagocytic Cells*, Editorial, J. A. M. A. **87**:306, 1926).

16. In recording the anatomic observations, a short clinical history is prefixed to every case considered.

The gross anatomic observations in the entire group were so stereotyped and devoid of striking differences that it is considered unnecessary to give detailed descriptions of the gross appearances in each individual case. It suffices to say that all the brains grossly examined were characterized by moderate increase in volume, by a varying degree of edema of the membranes and marked congestion of the pial and cortical blood vessels.

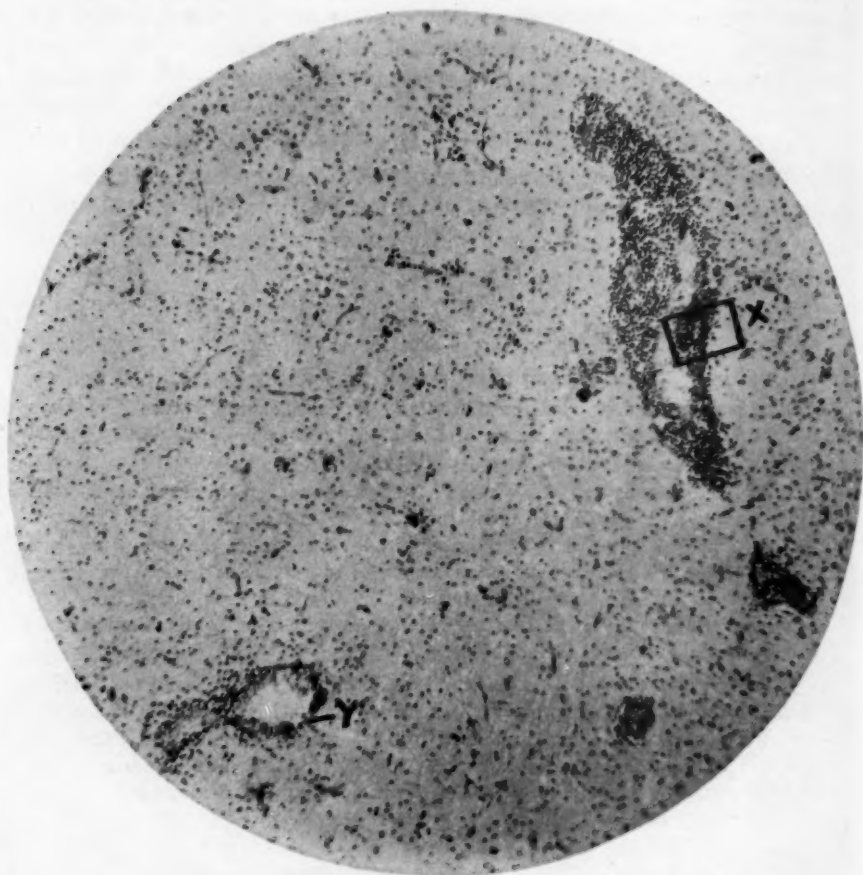


Fig. 1.—Low power field showing the size of the maximal perivascular infiltration (X is the field magnified in fig. 5). Focal infiltrations and lymphoid aspect of parenchyme should be noted, the latter due to streamlike orientation of lymphoid cells (Y); $\times 90$.

A departure is noted in only one instance: case 5383, so atypical in its minute anatomic changes, showed numerous punctate hemorrhages in the substance of the brain and its membranes.

In none of the clinical histories of the cases studied were facts of importance found in the family and developmental records bearing on the fatal illness; hence no reference will be made in the individual case records to family and past personal histories.

Initial infiltration was best observed in cross-sections of capillary tubes. Here (fig. 2) the cells were almost exclusively small lymphocytes, characterized by large, deeply staining nuclei and narrow rim of protoplasm. Their uniform marginal radial seriation argued strongly in favor of their hemic origin, and lymphocytes could be seen actively emigrating; figure 3 *A* shows emigrating lymphocytes (*em. l.*) in transit through the capillary wall and in fig. 3 *B.*, *a* has just left the capillary wall, and *b* is obviously migrating into the tissue.

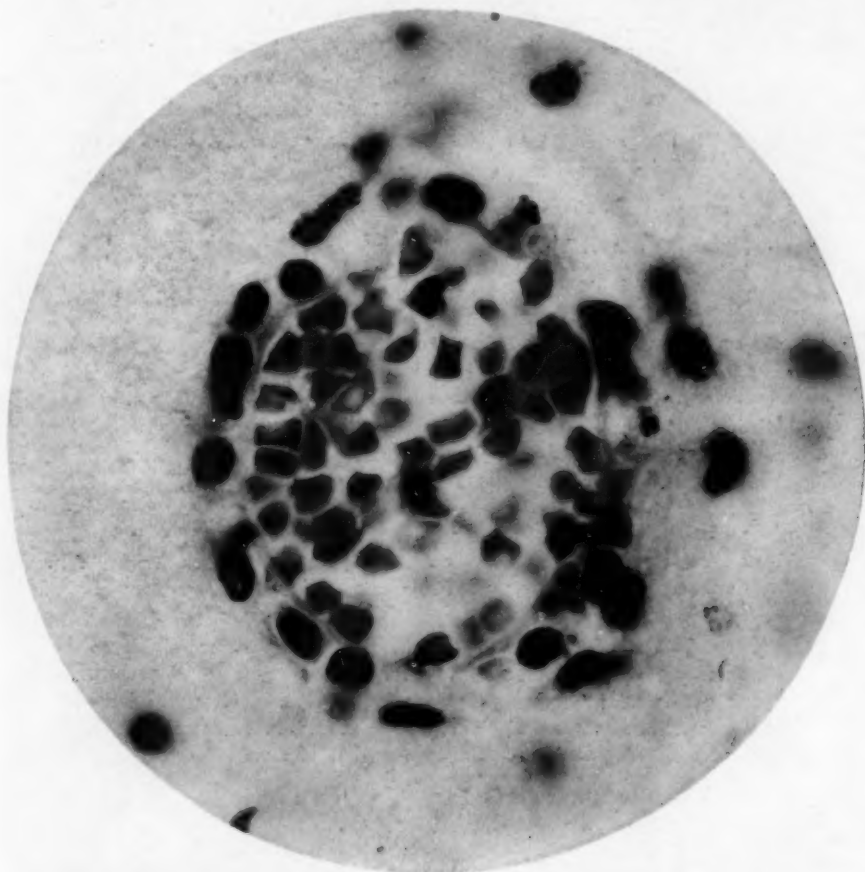


Fig. 2.—Capillary, showing marginal radial seriation of lymphoid cells—an initial stage of infiltration; $\times 1325$.

With progressive differentiation capillaries were found with two marginal rows of cells, the inner consisting predominantly of small lymphocytes; the outer, of medium-sized, i.e., hypertrophying, lymphocytes.

In infiltrations made up of three or four rows (fig. 3 *C* and fig. 4), the inner cells were predominantly small lymphocytes; the outer, hypertrophying individual cells, some of which had reached the size of typical large mononuclears or so-called "endothelial leukocytes." The transition stages between the small lymphocytes and the large mononuclears were remarkably clear and frequent.

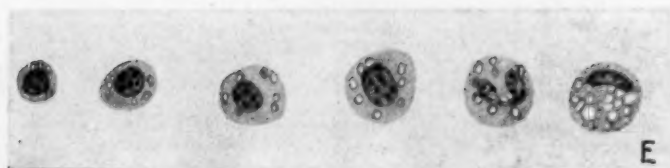
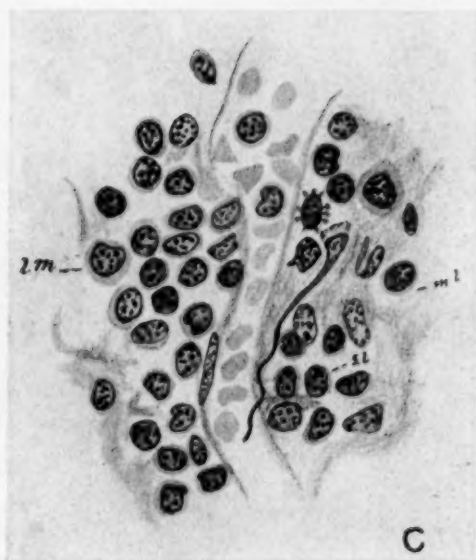
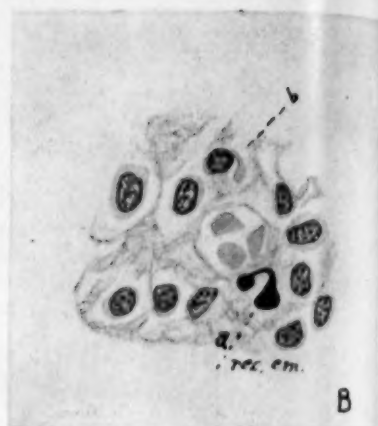
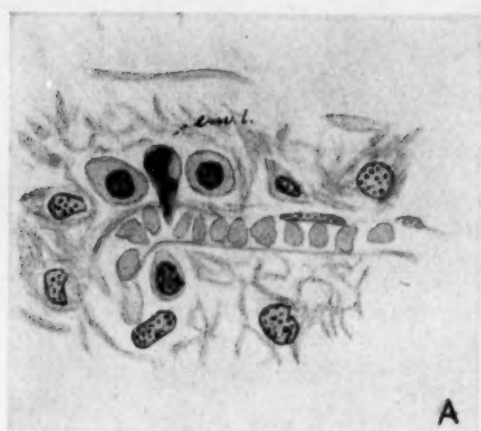


Fig. 3.—All figures were drawn with the camera lucida at the same magnification. Zeiss homogeneous oil immersion $\frac{1}{2}$ objective; compensating ocular, $\times 10$.

- A, Capillary showing an emigrating lymphocyte (*em. l.*). Adjacent hypertrophying individual cells should be noted.
- B, Forms assumed by emigrating lymphocytes: migrating individual cells (*a, b*); a few others are undergoing hypertrophy; recently emigrated lymphocytes (*rec. em.*).
- C, Fig. 7 shows the same emigrating large mononuclear (*l. m.*). The drawing shows the complete tail-like protrusion of the nucleus, not seen in the photograph. Total cell length, 33 microns.
- D, Forms assumed by an emigrating lymphocyte (*em. l.*); division of a mononuclear cell (*m. l. m.*) in extravascular habitat is seen.
- E, A series of stages of cells indicating heteroplastic development of the so-called "gitter cells" from lymphocytes; hypertrophy, vacuolization and displacement of nucleus is shown.
- F, Dumbbell-shaped, recently extravasated large mononuclear (*rec. em.*). Also a macrophage (*mac.*) engulfed lymphocyte (*mac.*).

The large mononuclears seen in the inner row were most likely either instances of immediate growth on the part of small lymphocytes after diapedesis or evidence of a direct extravasation of large mononuclears.

In some of the larger infiltrations of from eight to fifteen rows (fig. 1, X, shown also under high power in fig. 5), the vast majority of the cells were small and medium-sized lymphocytes, perithelially situated large mononuclears being relatively few in number. In others, especially those about the larger veins, the predominating type of cell was that of the medium-sized lymphocytes and large mononuclears. That many of the latter were of hemic origin was evidenced by the high rate of identical cell types present inside and outside the vessel lumen.

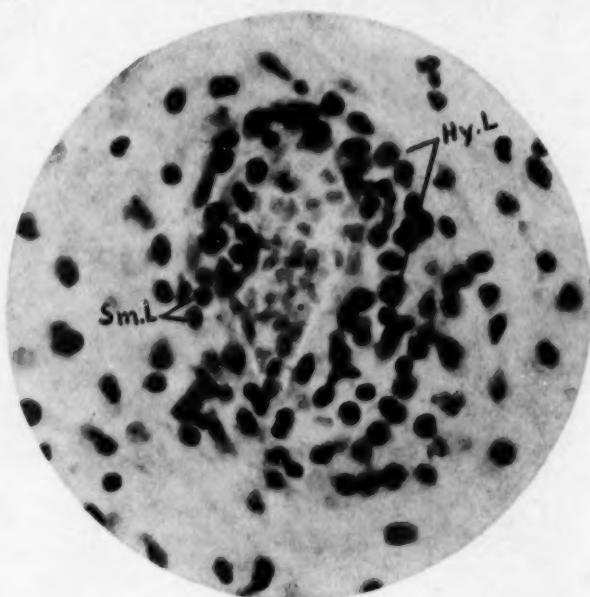


Fig. 4.—Vessel with three or four rows of lymphoid cells, the inner consisting predominantly of small lymphocytes (*Sm. L.*). Hypertrophying individual cells (*Hy. L.*) toward the periphery; $\times 600$.

In perivascular areas, the hypertrophy or change from small lymphocyte to large mononuclear was rather stereotyped. During the process the nuclei of the small lymphocytes lost their dense and basophilic aspect, their chromatin network became more open, revealing with distinctness a varying number of angular blocks. The nuclear polymorphism they assumed attested their ameboid movement.

The hypertrophy involved a corresponding change in the cytoplasm. Restricted to a narrow, slightly basophilic rim in the small-sized lymphocytes (fig. 3 C), it became larger, more deeply basophilic and more abundantly vacuolized. That some of the large mononuclears had phagocytic properties, i.e., had been transformed into macrophages, was evident from the small lymphocytes engulfed in their protoplasm.

Emigration: In all the foregoing types of infiltration, emigration of lymphoid elements was observed. Sparse about the wall of capillary tubes, they became more numerous in larger vessels, around which there were commonly three or four rows, although there were as many as from eight to fifteen in some places.

At times extravasation was accomplished with but slight change in cell area and morphology (fig. 3 A and fig. 6); at other times both cytoplasm and nucleus

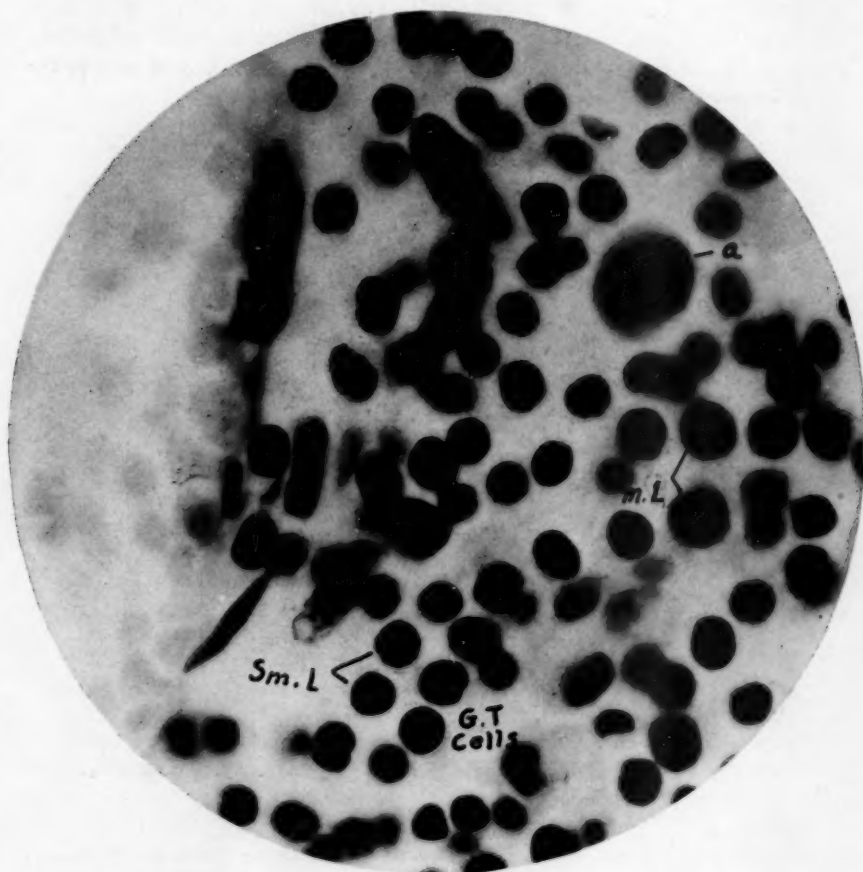


Fig. 5.—High power view of field in fig. 1 marked X. Note predominance of small lymphocytes (*Sm. L.*); many medium-sized (*m. L.*) individual cells; a binucleated structure (*a*); and granular "gitter" cells (*G. T. cells*); $\times 1,500$.

were drawn out into long irregular structures, the advancing portion of the cell containing the main mass of cell content (fig. 3 C, and figs. 7 and 8). In figure 8, the cell measured 15 microns in length; in fig. 7, 33 microns, with a portion of the flagellum-like extrusion of the nucleus still present in the vessel lumen as pictured in figure 3 C. The cell shown was a typical blood mononuclear and demonstrated the direct hematogenous origin of at least some of the so-called "endothelial leukocytes" encountered.

Small and medium-sized lymphocytes in transit through the capillary wall assumed such a pronounced degree of basophilia as frequently to obscure all traces of cytoplasm. Hence dark round masses with pronounced pseudopods ending in rotund fashion (fig. 3 *B* and *D*) in juxtaposition or in contact with the endothelium were considered as emigrated lymphocytes and not as tangential sections of endothelial cells (Marcora). Such transitory lymphocytes could be seen in small capillary tubes showing perfect unbroken endothelium near which were found previously extravasated migrating and dividing free cells (fig. 3 *D*).

Curved, dumbbell-shaped, deeply staining nuclei with clear-cut cytoplasmic contours, seen frequently outside the vascular endothelium (fig. 3 *F*, and fig. 9), were not desquamated endothelial cells, but represented recently emigrated lymphocytes or large mononuclears. Thin strands of nuclear material running from the

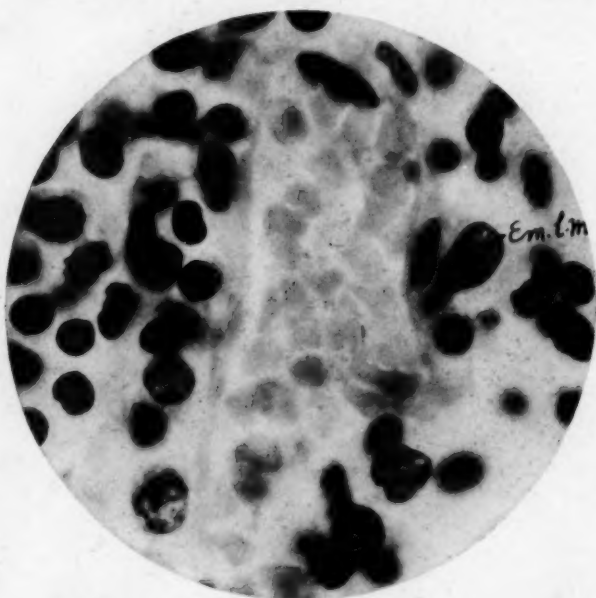


Fig. 6.—Flask-shaped emigrating large mononuclear (*em. l. m.*); $\times 1,325$.

capillary lumen to a main cell body located in the third or fifth row of lymphocytes indicated clearly that the emigration process was at times slow and arduous.

Infiltrations in Extravascular Territory: In the case under consideration, the parenchyme was diffusely populated by many migrating lymphoid cells of which more dense aggregations were noted in centers of intense glia activation and mobilization (fig. 10).

Although some of such wandering cells in the tissue had probably originated from pre-existing lymphocytes by way of mitotic division, a vast majority of them had come from the blood stream. Relatively few and isolated in the neighborhood of capillary tubes, migrating lymphocytes became more numerous with increase in the depth of vascular infiltration and in the highest types of the latter, there was a marked streamlike orientation and migration of cells away from the wall of the vessel (fig. 1, with *Y* magnified in fig. 11).

After leaving the vascular area, lymphocytes usually hypertrophied into a cell type resembling the histiocytes or polyblasts of Maximow. Its frequent irregularity of cytoplasmic contour, deep basophilia and rather stereotyped small vacuolization were sufficient criteria to distinguish it from the adjacent glia cells.

Not all of the emigrated cells underwent hypertrophy, with the result that small and, more often, medium-sized lymphocytes were seen frequently at con-

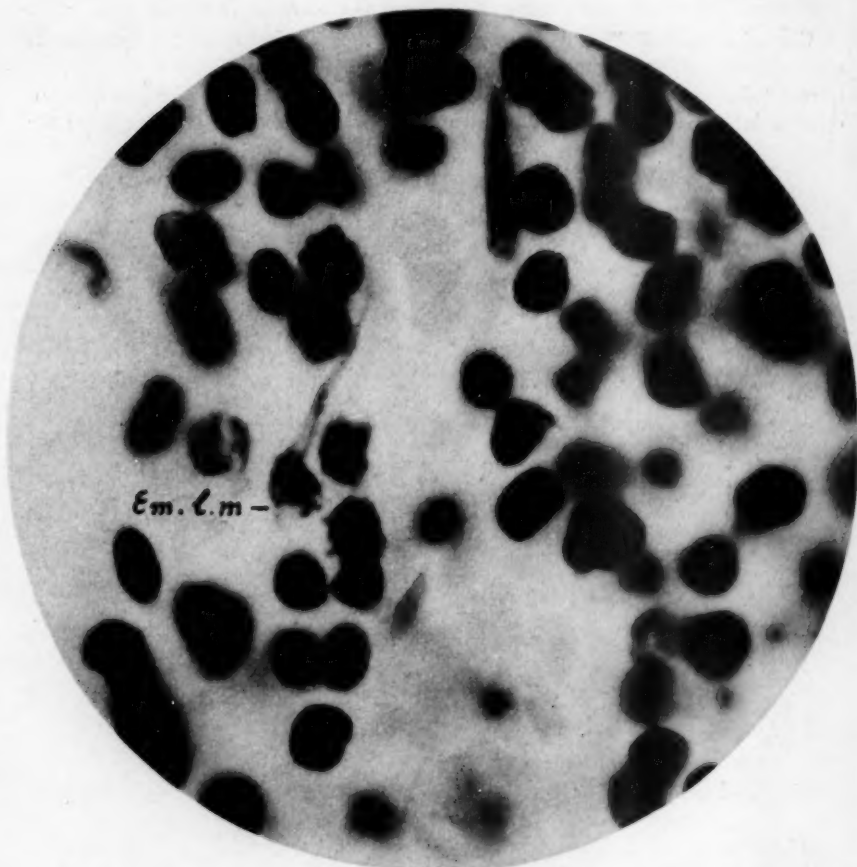


Fig. 7.—A photomicrograph of the emigrating large mononuclear (*em. l. m.*) pictured in fig. 3 C. A portion of the flagellum-like protrusion of nuclear material is not shown here, since it lay in a different plane; length, 33 microns; $\times 2,000$.

siderable distances from the blood vessels (fig. 12). Incidentally, such types of cells could be distinguished from the adjacent glia cells by the fact that the nuclei of the former stained more deeply, had a more abundant chromatin network, the meshes of which showed distinct angular block formations. Glia nuclei were usually round or oval and showed less abundant chromatin arranged in small but numerous, uniformly distributed spherical particles. (This observation does not include the so-called microglia, the nature of which was still under discussion.)

With increased ameboid activity, some of the glia cells frequently assumed a decided polymorphism, but even in that state they could readily be distinguished from the migrating lymphocytes.

Binucleated elements (fig. 5 a) were frequently encountered. They cannot be interpreted with certainty, but they may be due to a fusion of two polyblasts or present a section of a highly polymorphonucleated cell type or not unlikely be a stage in cell division.

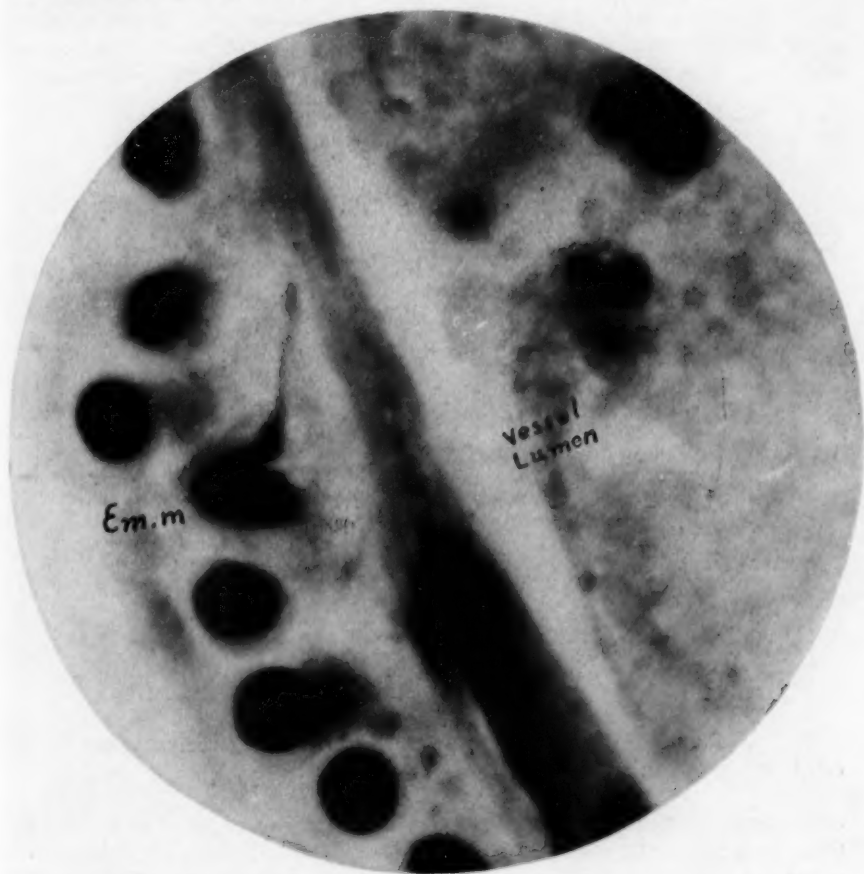


Fig. 8.—Another instance of an emigrating large mononuclear (*em. m.*) with a tail-like pseudopod following the main mass of advancing protoplasm; length, 15 microns; $\times 2,500$.

Compound Granular Cells ("Gitter" Cells): In addition to the many diffusely distributed migrating lymphocytes, histiocytes and polyblasts, the parenchyma showed at frequent intervals local, fairly circumscribed aggregations of free cells (focal infiltrations) intermingled with highly active and ameboid glia cells (fig. 10). Such centers gave a superficial resemblance to the "taches laiteuses" of the omentum. Whether entirely free from blood vessels or in direct contact with capillary tubes, such centers consisted of small and medium-sized lympho-

cytes, free histiocytes and polyblasts, some of which were in mitotic division, while others were in the "binucleated" condition. The interspersed glia cells presented an extremely irregular nuclear and cytoplasmic morphology, with some of the cells rounding up from the general neuroglia network, surrounding themselves with a mass of protoplasm which progressively became more vacuolated and of a more even contour, and ending in the formation of the so-called compound granular cells ("gitter" cells).

In the free and completely differentiated condition these granular cells (gitter cells), as a rule, attained the size of the large mononuclears, though smaller individual cells were encountered (fig. 13). Their nuclei, while occasionally still round and central in position, in the majority of instances were kidney-shaped



Fig. 9.—Photomicrograph of the recently emigrated large mononuclear (*rec. em. l. m.*) drawn in fig. 3 F; $\times 1,750$.

and eccentric. The protoplasm showed a relatively large number of vacuoles, at times uniformly small, at times decidedly varied, a few large ones occupying most of the cell area. In a few instances compound granular cells showed phagocytic activity engulfing lymphocytes and red corpuscles (fig. 13).

Formation of granular cells was also observed outside of these lymphoid foci. Areas were encountered in which several adjacent microscopic fields were occupied almost exclusively by compound granular cells (fig. 13). Usually, the more prevalent the latter, the less frequent were the fixed and the intact glia cells.

That at least a portion of the compound granular cells were derived directly from emigrated lymphocytes and histiocytes was obvious from the many intermediate stages seen between small lymphocytes and the fully differentiated cells, which were morphologically indistinguishable from those of neuroglial origin. This transformation of emigrated lymphocytes into granular cells is gradual

and is seen in the increase of the size of the cell accompanied by a progressive vacuolization of cytoplasm, an indentation and final eccentric displacement of the nucleus.

Grouping of compound granular cells around endothelial tubes and precapillary venules was frequently found. While this of itself did not necessarily prove a hemic origin for the entire group of granular cells, it lent support to other

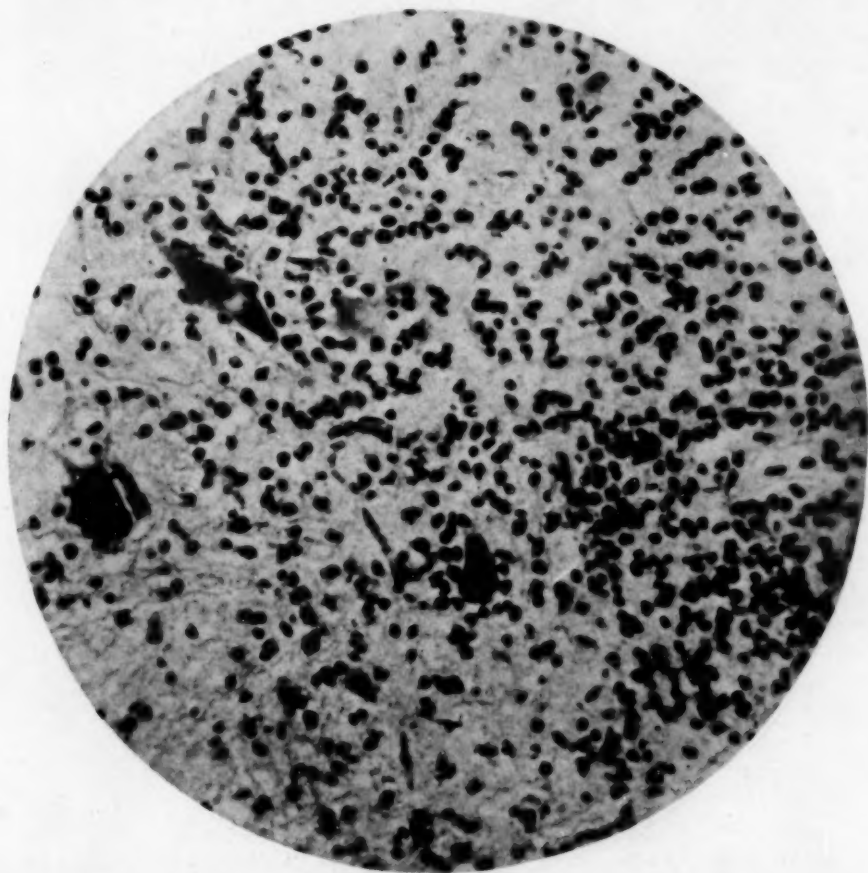


Fig. 10.—Field showing focal infiltration, interspersed migrating lymphoid cells, capillaries and degenerating ganglion cells; $\times 300$.

evidence favoring our belief, that at least some of them originate from elements which have recently left the blood stream, (fig. 13).

Miscellaneous Observations.—In a few instances the perivascular infiltration was strikingly rich in polymorphonuclears (fig. 14). Many of the latter showed partial hypertrophy and ameboid activity in the adventitial space, but relatively few had migrated out into the general parenchyma (extravascular territory).

Eosinophils were so remarkably rare among the cells of infiltration as to warrant the conclusion that as a cell type, they did not take part in the inflammatory process.

Extravasation of red corpuscles, on the other hand, was rather common and was noted in nearly all the vessels. As a rule, the greater the perivascular infiltration, the larger is the number of erythrocytes noted. At times the latter were interspersed with the lymphoid elements in the adventitial coat; at times hordes of red corpuscles became lodged close to the periphery of the infiltrating mass. The frequent open breaks in the endothelial wall explained the manner of their leaving the blood stream.

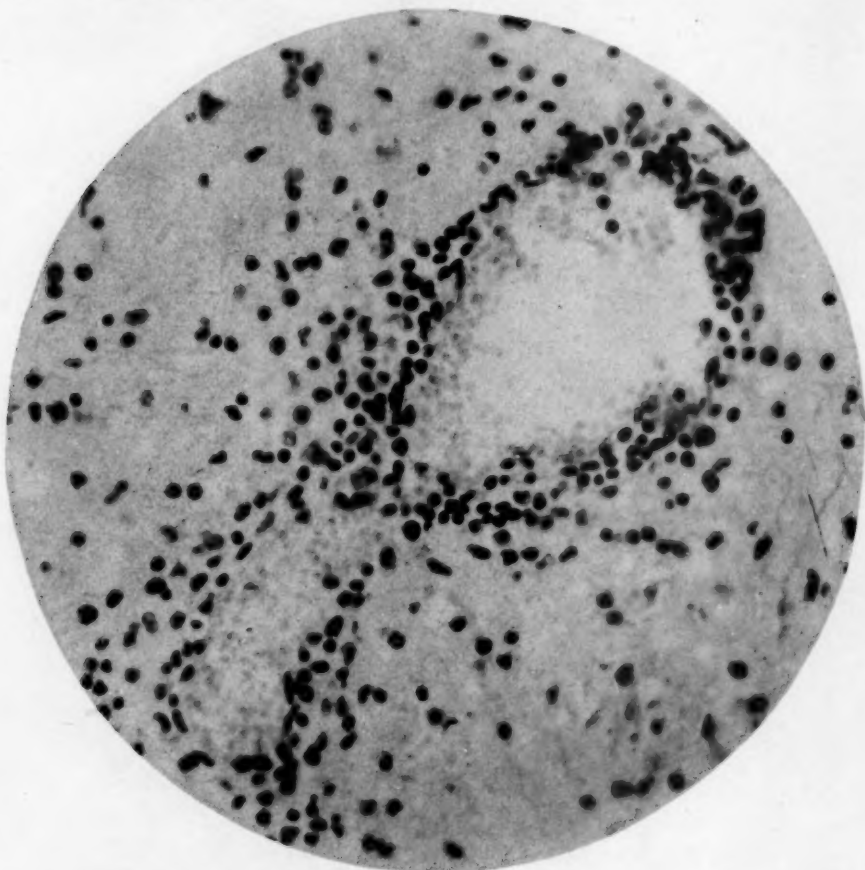


Fig. 11.—High power view of field Y in fig. 1, showing streamlike orientation and migration of lymphoid cells away from the blood vessels; $\times 400$.

In certain instances the degree of extravasation of red corpuscles was so pronounced as to constitute a diffuse flow of the blood stream into the parenchyma proper, thus forming punctate hemorrhages. Hemorrhagic areas not unlike similar foci in other lesions of the brain caused subsequent activation, mobilization of glia cells and ultimate transformation of such cells into the granular cells.

Sections stained with Mallory's connective tissue stain showed that with increase of perivascular infiltration there was a corresponding increase of collag-

enous fibers (fig. 15). In the same photomicrograph may be seen a giant cell with four overlapping nuclei, a cell element extremely rare in all the cases studied.

Of primary importance from a cytogenetic point of view is the noteworthy observation that in not a single instance beginning with initial one-row infiltration to the highly advanced type of from eight to fifteen rows was the vascular endothelium instrumental in the production of free cells, either by desquamation or mitotic proliferation. Save for occasional breaks, the entire endothelium was perfectly normal and inactive. This observation invalidates to a large extent Foot's recent contentions as to the endothelial origin of the large mononuclears or so-called endothelial leukocytes.

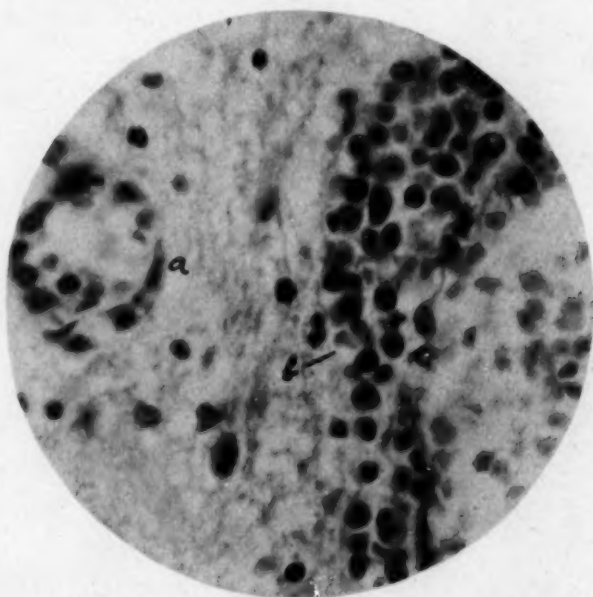


Fig. 12.—An initial (*a*) and a somewhat progressed (*b*) type of infiltration. In the latter note emigrating large mononuclear and migrating lymphocytes at considerable distances from the vessel wall; $\times 650$.

A local origin of free lymphoid cells from Marchand's adventitial cells, so frequently reported in the literature, was not observed. Observations from the present material allowed the interpretation of the oblong cells with lymphoid aspect skirting the wall of the vessel, which were to a large extent emigrated, hypertrophying lymphocytes. They presented remarkably clear and frequent transition stages. Finally, mitotic figures, while frequent in the round lymphoid cells, were scarce or entirely lacking in the oblong type.

Since there was no evidence that other perivascular connective tissue elements, especially those of the adventitial coat, were instrumental in the production of free lymphoid cells, the assumption seemed justifiable in this case that the vast majority of the cells found in the perivascular infiltration originate directly from the blood stream, with some formed locally through mitotic proliferation of pre-existent or previously extravasated lymphocytes.

CASE 2.—*History*.—D. W., a boy, aged 6, was admitted to the hospital on Sept. 11, 1925. Four days prior to admission to the hospital, the patient fell down a flight of stairs. Direct ill effects were not apparent. The next day, however, he began to complain of headache and pain in the back. There was a moderate rise in temperature. Shortly afterward, he began to complain of inability to stand. This weakness in the legs progressed, and on the day preceding admission, complete paralysis of both legs and weakness of the arms appeared.



Fig. 13.—A field of granular cells, some of which originated heteroplastically from lymphocytes as proved by the intergrades seen. Granular macrophages, one with engulfed lymphocyte (*a*); the other with a red blood corpuscle (*b*), are shown. Average size of granular cell, 10 microns. This figure should be compared with figure 3 E; $\times 1,000$.

On the day of admission he began to experience difficulty in speech, which was soon followed by almost complete loss of articulation.

Examination showed paralysis of the left external rectus muscle, weakness of the motor branch of the fifth nerve and complete loss of power in all four extremities. All deep reflexes were absent.

Progress of the disease was rapid, bilateral ptosis appearing in addition to the foregoing observations. The spinal fluid was under increased pressure, with 210 cells (lymphocytes) per hundred cubic centimeters, and the child died. The clinical diagnosis was polio-encephalomyelitis of bulbar type, and the anatomic diagnosis was polio-encephalomyelitis.

Microscopic Examination.—In this case of polio-encephalomyelitis, the perivascular infiltration was again pronounced, averaging from three to five rows for

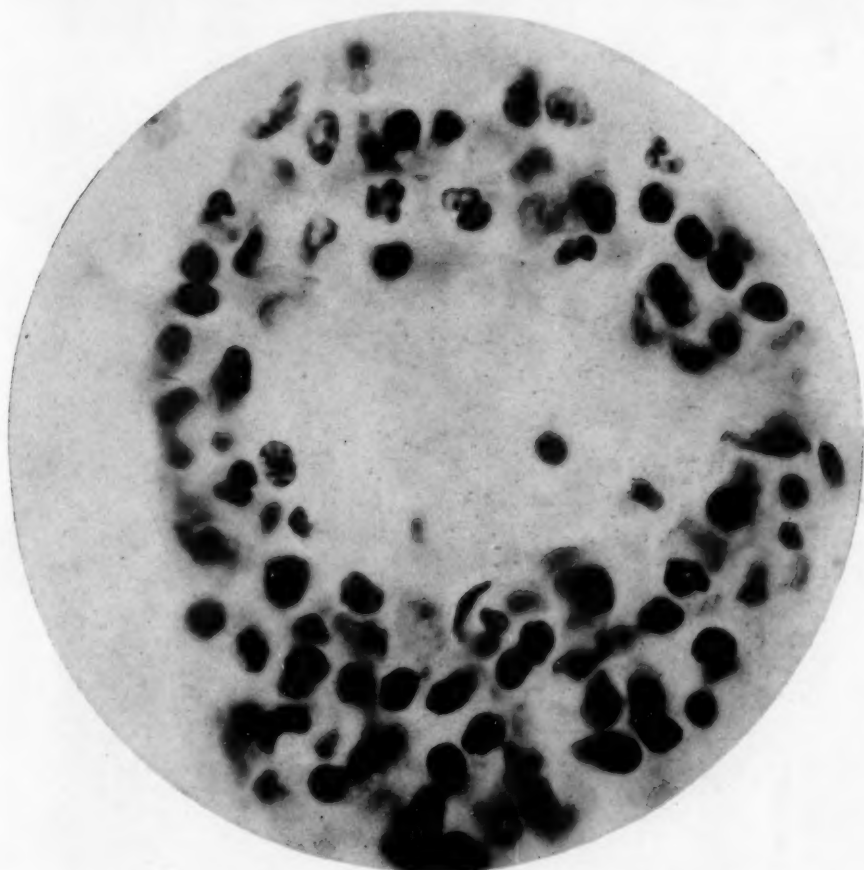


Fig. 14.—A vessel showing a massive extravasation of polymorphonuclear leukocytes; $\times 1,325$.

most vessels with capillaries showing a minimum of one or two rows and the larger vessels a maximum of nine or ten rows. The parenchyme, although showing many migrating free cells, was not so lymphoid as in the previous case.

Initial infiltration was best observed in sections of precapillary venules. The marginal cells were lymphocytes, some of which had hypertrophied and given rise to oblong, box-shaped structures, which might be erroneously taken for Marchand's adventitial cells.

In infiltrations of two or three rows the majority of the cells were small lymphocytes; some were medium-sized with only a few large mononuclears scattered among them. The direct hematogenous origin of some of the latter is shown conclusively in figure 16, *B C D E*. Figures 17 and 18 and *A* and *C* in figure 16 show lymphocyte emigration.

In vessels with larger infiltrations, the mononuclears or so-called "endothelial leukocytes" were much more numerous than in case 2. Owing to a marked ameboid activity, their nuclei were often indented, lobulated and at times almost entirely segmented into two chromatin masses, thereby giving rise to the binucleated elements so frequently encountered in this case (fig. 16 *D*). The cytoplasm of the mononuclears often showed a pseudopod formation and a

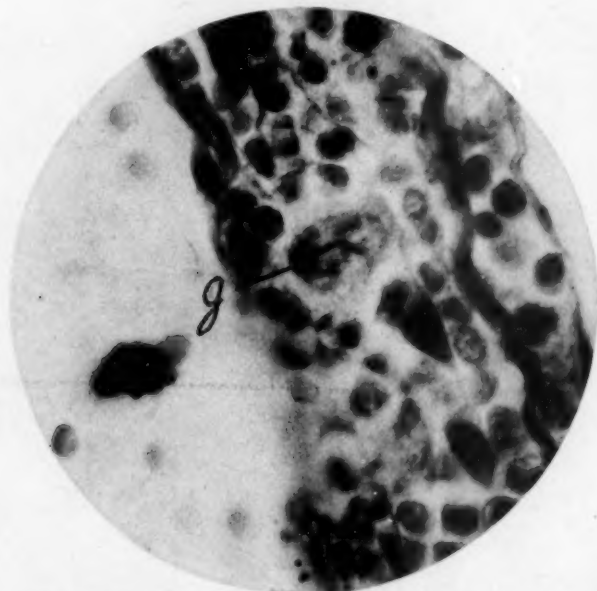


Fig. 15.—Giant-like cell (*g*) with overlapping vesicular nuclei (uncommon in material studied). Increase of collagenous fibers shown; Mallory's stain; $\times 1,000$.

much more frequent and more pronounced vacuolization than in the small and medium-sized lymphocytes.

Variations in basophilic tendencies were noted among the large mononuclears, some of which were deeply basophilic, containing dark nuclei, while others had relatively lighter staining protoplasm and nucleus (fig. 16 *A*). Since intergrades were present, this difference in basophilic reaction may be regarded as indicative of a temporary physiologic change, rather than of a difference in the origin of the cells involved.

Decidedly more frequent than in the preceding case was the transformation of large mononuclears into macrophages, the cell body of the latter containing from one to three engulfed lymphocytes (fig. 3 *F*).

So in this case also, we believe that the vast majority of the perivascular lymphoid cells were emigrated large mononuclears and emigrated lymphocytes

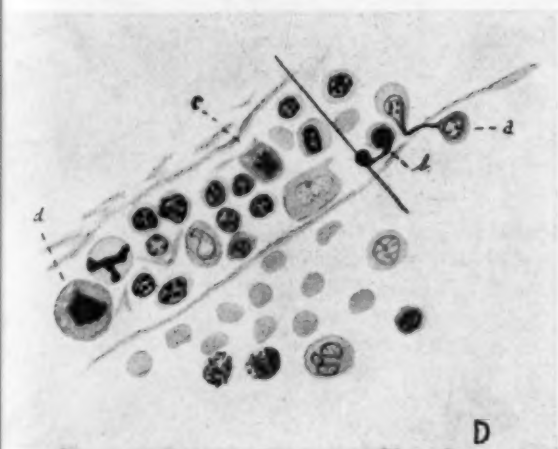
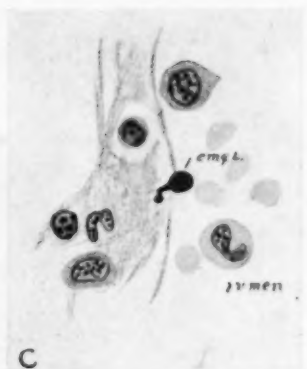
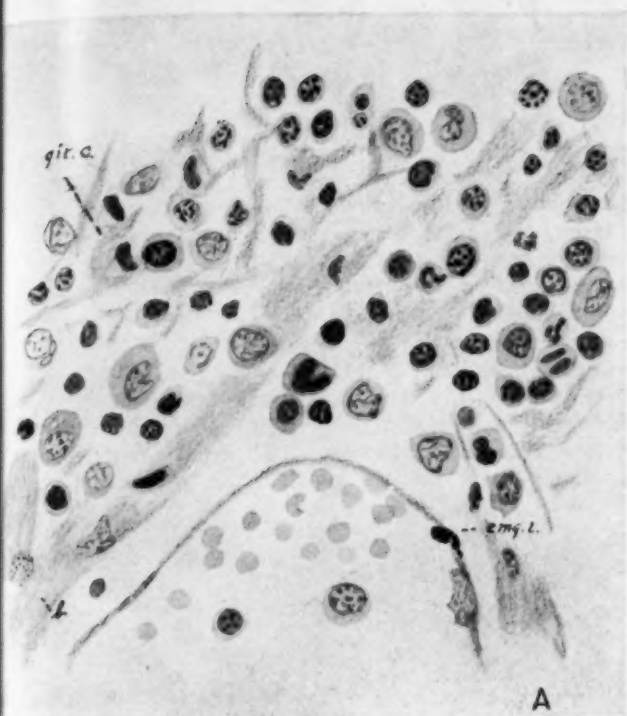


Fig. 16.—A, Field showing various types of infiltrating cells. Note the emigrating lymphocyte (*emg. l.*); the "gitter," or granular cell (*git. c.*); the polymorphonuclears and the transition stages between small lymphocytes and so-called "endothelial leukocytes" or large mononuclears. The latter should be compared with the types present in the lumen.

B, A large mononuclear in transit through the vessel wall (*em. l. m.*), showing advancing cytoplasm. The same cell was photographed in figure 18.

C, Form assumed by an emigrating lymphocyte (*emg. l.*).

D, A composite field, as indicated by the line drawn, obtained from two areas of the same vessel, showing an emigrating large mononuclear (*a*); a recently emigrated small lymphocyte (*b*); a dividing medium-sized lymphocyte (*c*); a dividing large mononuclear (*d*). Extravasation of red corpuscles was also noted.

E, Flagellum-like protrusion of nuclear material during the emigration process (*flg.*).

with their derivatives, which assumed new forms by hypertrophy and through mitotic division. This was clearly seen in figure 16 *D*, in which *a* represents a large mononuclear in transit through the wall of the vessel; *b* a recently emigrated lymphocyte; *c*, a dividing medium-sized lymphocyte, and *d*, a dividing large mononuclear.

As noted in the preceding case, transit through the wall of the vessel involves a characteristic nuclear elongation and contortion of cell body producing frequently a structure not unlike that of a bent dumbbell (fig. 16 *B* and *D* and fig. 18). That this shape may temporarily be retained even after extravascular habitat is clear from figure 3 *F* and figure 9. Forms assumed by emigrating lymphocytes are pictured in figure 16 *A*, and in figure 19.

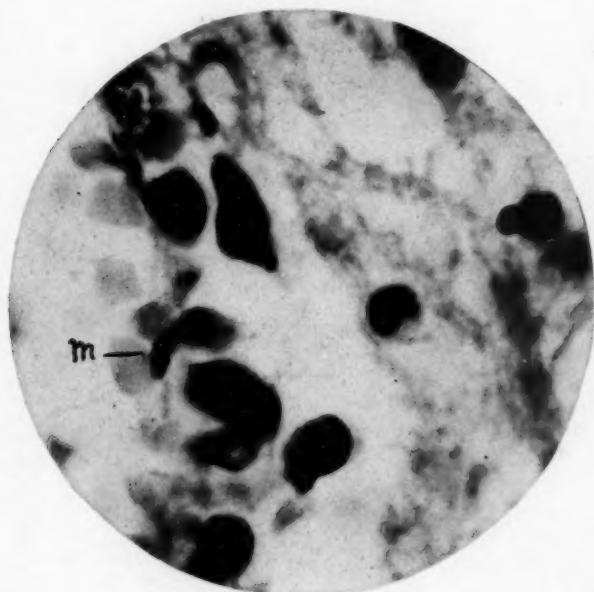


Fig. 17.—A clear demonstration of the direct hemic origin of the so-called "endothelial leukocyte;" a blood mononuclear is seen in transit (*m*); $\times 1,750$.

While at times the cytoplasm is clearly discernible in emigrating medium-sized lymphocytes (fig. 16 *B*), it is usually not visible in small lymphocytes (fig. 16 *A*). Structural changes in emigrating large mononuclears are depicted in various stages in figure 16 *D*. It should be borne in mind that in the study of the migration process of lymphocytes and large mononuclears, change of focus is often necessary, since, because of contortion of the cell in progress of migration, the distal ends may become lodged in two different planes. Then again in thin sections, the emigrating cells may frequently be cut in two and appear as disunited fragments. In spite of the large number of emigrating lymphocytes, the predominating cell type passing through the vessel wall is the large mononuclear, which explains the high ratio of this type of cell in the larger infiltrations (fig. 16 *A*).

The morphologic identity of the lymphocytes and large mononuclears in the perivascular habitat with those situated in the vascular lumen (fig. 16 *A* and *C*)

is another important observation in support of the immigrant origin of cells in the perivascular infiltrations.

In addition to the lymphoid elements, granular cells (gitter cells), varying in number, and fully differentiated (fig. 16 *A*), irregularly segregated and often vacuolated glia cells (*b*) and other glial elements, which we shall not discuss here, were present in the infiltration, especially in the more massive types.

Polymorphonuclears, some of which were extensively pigmented with hemoglobin particles, were also invaders of such exudates (fig. 16 *A*). Morphologically, they corresponded to those frequently found in the lumen of thrombosed vessels. Eosinophilic leukocytes and mast cells were rare, only a few individual cells being encountered.

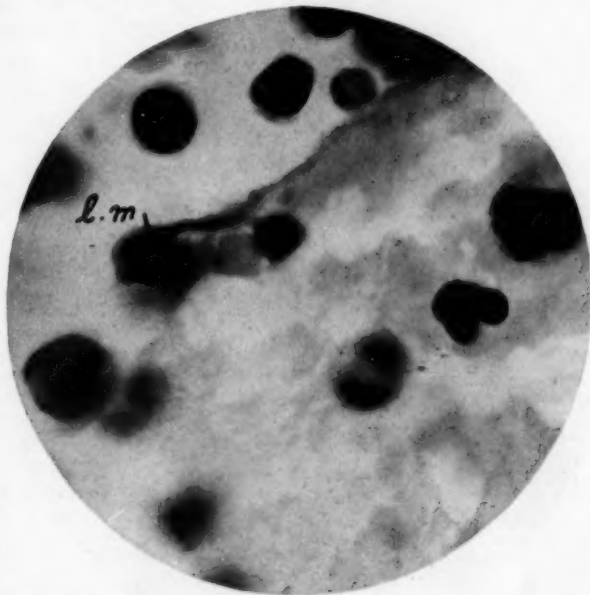


Fig. 18.—Photomicrograph of the cell drawn in fig. 3 *A*, showing a typical dumbbell-shaped migrating large mononuclear (*l. m.*). Size, 15 microns; $\times 1,750$.

Extravasation of red corpuscles was also general here, marked in some instances, meager in others. At intervals, open breaks in the endothelial wall of vessels led to more massive hemorrhages punctate in character and at distances from the blood vessels.

Extravascular Territory: Less lymphoid infiltration was found than in the preceding case; still the parenchyme showed an abundance of migrating lymphocytes, large mononuclears, histiocytes and polyblasts. That many of these were of hemic origin was evidenced by the streamlike orientation of intergrades noted in the neighborhood of vessels. That others arose homoplastically was clear from the mitotic figures encountered.

Grouping of lymphoid elements and glia cells in the fashion of "tâches laiteuses", so characteristic in the preceding case, was less pronounced and not so crowded. These areas of focal infiltration showed free cells (lymphocytes, histiocytes, polyblasts, some in division) with varying nuclear and cytoplasmic contours. The intermingled fixed glia cells were highly ameboid, their nuclei

often assuming a marked polymorphism, their protoplasm becoming irregularly vacuolated. At intervals dividing glia cells were found.

In certain areas the neuroglia tissue showed decided alveolarization; a part of the involved glia nuclei became polymorphic (i. e., ameboid); others degenerated or assumed deep pyknosis, while still others were surrounded with a mass of vacuolated protoplasm and gradually differentiated into free compound granular cells. The formation of the latter, however, was not so pronounced as in the preceding case. This finds a possible explanation in the fact that lymphocytes were not seen to differentiate into compound granular cells, as observed in the first case, and hence another source of origin was probably lacking. Finally a few isolated degenerating neutrophils with pyknotic nuclei were present, perhaps remnants of an earlier infiltration.

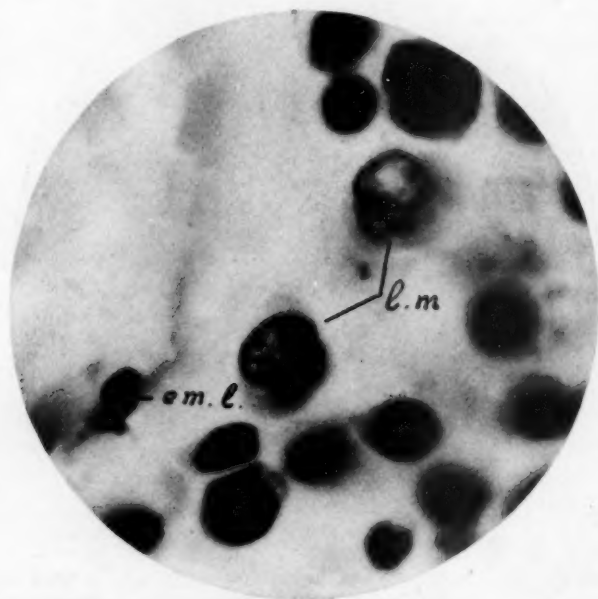


Fig. 19.—Photomicrograph, corroborating camera lucida drawing fig. 16 A, showing an emigrating lymphocyte (*em. l.*), which, because of variation in depth of focus is better shown in fig. 16, and two large mononuclears (*l. m.*) differentiating into polyblasts; $\times 1,750$.

As in the previous case, the vascular endothelium did not show mitotic proliferation or desquamation in a single instance. Save for occasional breaks, it was normal throughout. Of significance likewise is the fact that even the most detailed scrutiny failed to reveal any proliferative or cytogenetic activity on the part of local adventitial connective tissue elements, beyond a slight increase in the amount of collagenous fibers in thickly infiltrated vessels.

Spinal Cord: Examination of sections from the spinal cord revealed a perivascular infiltration similar to that observed in the brain. Emigrating and subsequently hypertrophying lymphocytes, direct emigration of large mononuclears, clustering and ameboid activity of glia cells and isolated formation of granular cells were found.

A final observation in this case was the excessive accumulation of pigment in nerve cells. The latter showed other evidence of initial necrobiosis.

CASE 3.—History.—K. I., a boy, aged 17, admitted to the hospital, Aug. 28, 1923, had suddenly had difficulty in swallowing and a disturbance in speech four days before. He entered the hospital in a moribund condition with marked difficulty in breathing. Shortly before the onset of the grave symptoms, he complained of pain in the throat and vomited several times. The left side of the face was weak; the tongue could not be protruded beyond the line of the teeth. The palate was immobile, and speech was thick. All deep reflexes were present and equal. Abdominal reflexes, except for those of the lower right quadrant, were present. The patient died within one hour after admission to the hospital.

The clinical diagnosis was polio-encephalomyelitis, bulbar type, and the anatomic diagnosis was polio-encephalomyelitis.

Microscopic Examination.—The sections from the brain were characterized by a pronounced, closely packed perivascular infiltration, at times reaching from ten to fifteen rows, and a parenchyme, which was decidedly less lymphoid than that in the two preceding cases. In vessels showing four or five rows (the average), the majority of the cells were small lymphocytes; next in abundance were the medium-sized lymphocytes, which frequently showed vacuolization and ameboid processes. Large mononuclears approaching the "endothelial leukocyte type" were frequently seen, from eight to ten being found in a single oil immersion field. Their morphology was stereotyped. Some of them were phagocytic, their protoplasm containing at times from one to four lymphocytes, at times engulfed polymorphonuclears or red corpuscles.

In the larger vessels, the ratio of large mononuclears and macrophages was decidedly higher. Such vessels showed increase of the collagenous fibrous network and many cytogenetic inactive connective tissue cells.

In some of the precapillary venules oblong, spindle-shaped lymphoid cells not unlike the so-called adventitial cells, instead of being parallel to the wall of the vessel, were at right angles to them, an indication that they were probably emigrated metamorphosing lymphocytes (polyblasts).

Active emigration pictures were rather rare; instead, the vascular lumina were frequently gorged with large mononuclears and small and medium-sized lymphocytes. Streams of morphologically identical cells, occasionally seen in the vicinity of blood vessels, served as evidence of the hemic origin of some of the free wandering lymphoid cells encountered in the parenchyme.

Mitosis of lymphocytes and large mononuclears was rare. Extravasated eosinophils were uncommon.

Extravascular Territory: Circumscribed areas of glial activity and mobilization were numerous, at times small, at times extensive. In the latter, the free granular cells predominated, with many glia cells on the road to differentiation. Their nuclei were becoming displaced and their cytoplasm was undergoing vacuolization, while the cell bodies were still irregularly attached to the neuroglia syncytium. At intervals in the meshes of the latter, small and medium-sized lymphocytes and polyblasts were seen.

A heteroplastic differentiation of compound granular cells from emigrated and subsequently hypertrophied lymphocytes was also noted, though not so frequently.

Extravasation of red corpuscles was nearly ubiquitous and extensive, at times reaching hemorrhagic proportions. A noteworthy difference was the diffuse mosaic-like distribution of erythrocytes in certain regions.

The lumina of certain vessels showed an abundance of pigment, at times free in the plasma, at times engulfed in polymorphonuclears and large mononuclears.

Spinal Cord: The type and high degree of glia activity in the cord was unique and extraordinary, almost completely obliterating its normal landmarks. Viewed under medium power (fig. 20), field after field consisted of free, densely packed, phagocytic glia cells alongside of widely dilated capillaries, heavily gorged

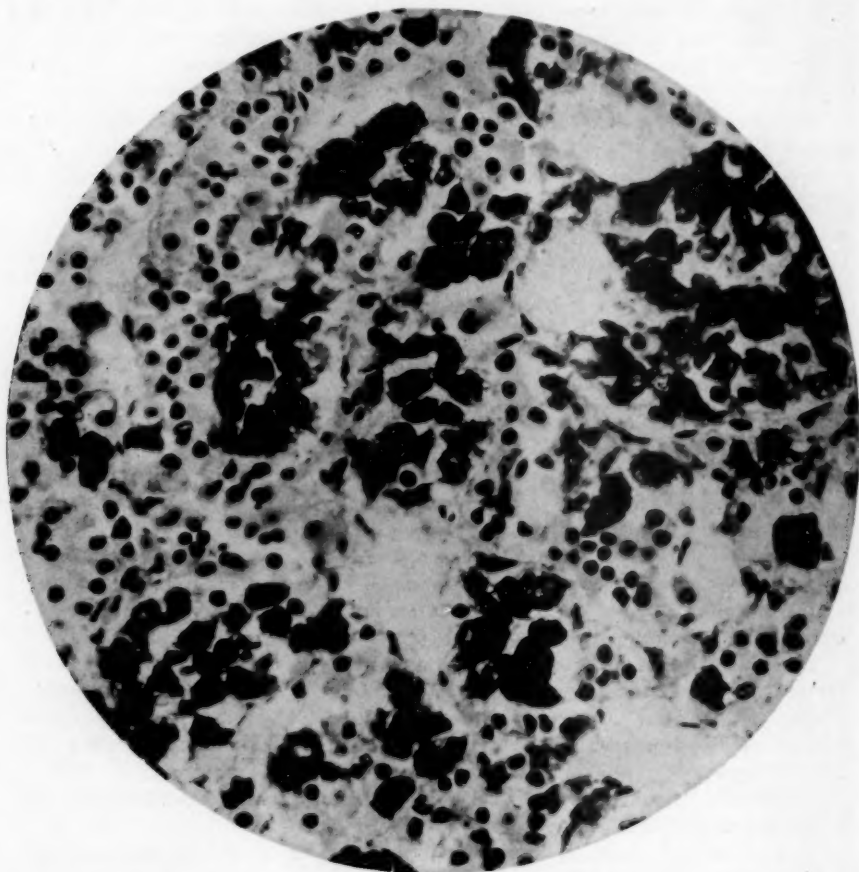


Fig. 20.—Spinal cord. Field in which the majority of the cells are free granular cells (dark nucleus, light cytoplasm). The large black structures represent deep basophilic granulated free granular cells or fixed glia cells; $\times 400$.

with blood. These phagocytic glia cells differ from granular cells, in that their nuclei are central instead of being eccentric, and that their cytoplasm is of even contour in rotund fashion, highly acidophilic, extremely granular and only slightly vacuolated. In a few of these cells acidophilia was so pronounced as to give a pink tone of an intensity greater than that in the adjacent red corpuscles.

Among this mass of free granular cells were many irregularly distributed foci of deeply staining, glia cells of uneven contour, showing a typical basic

granulation, not unlike that obtaining in tissue mast cells (fig. 20). Save for the metachromatic staining reaction of the latter, the granules were morphologically uniform and, as in the mast cell, frequently "trailed" the cells as isolated granules or were encompassed in bits of irregularly shaped protoplasm which anastomosed with those of adjacent similarly granulated cells.

In such completely rounded up cells (fig. 20), the basic granulation was frequently so dense and abundant as to obliterate all traces of nuclear morphology; in others, the granules were aggregated to one side of the cell body uncovering the glia nuclei, which was at times vesicular or again nearly normal.

That the cells in question were liberated and transformed glia elements was obvious from the many intergrades found, which presented various stages with a progressively increasing type of basic granulation. Vacuolization of protoplasm, while abundant and general in the less differentiated cells, was usually restricted to a single vacuole in the fully rounded, spherical basic granulated individual cells.

Despite the high ratio of free cells, traces of neuroglia fibers and occasional unmodified glia cells were encountered in various regions.

The numerous capillary tubes, engorged with red corpuscles, were frequently devoid of lymphoid elements; the latter were likewise remarkably sparse in perivascular areas, as though the infiltration process had occurred early and seemingly brought to completion a conclusion favored by the fact that emigrating cells were rarely seen, and morphologically modified lymphoid cells (histiocytes, polyblasts) were only occasionally encountered in regions distant from the blood vessels.

CASE 4.—History.—P. F., a boy, aged 14, admitted to the hospital, Aug. 23, 1923, had begun to complain of headaches and generalized malaise two days before, and his temperature had risen to 102 F. The following day he complained of weakness in an arm and leg and some harshness of his voice.

The patient was alert and somewhat irritable and his voice was high-pitched. There was slight bilateral ptosis, weakness of the fifth motor nerve on the right side, facial weakness on the right side. The tongue deviated to the left. All upper deep reflexes were diminished, while the knee jerks and ankle jerks were exaggerated. The abdominal reflexes were diminished. Flaccid paralysis of the right arm, paresis of the left arm and weakness of the muscles of the neck were present. The spinal fluid was under increased pressure, with 90 lymphocytes per cubic centimeter. He declined rapidly, and death occurred on the third day.

The clinical diagnosis was polio-encephalomyelitis of the high bulbar type. The anatomic diagnosis was polio-encephalomyelitis.

Microscopic Examination.—The nature and degree of perivascular infiltration were not unlike that seen in the previous cases. It was incipient, with one or two rows of lymphoid cells in precapillary venules. The infiltration in the larger veins reached an average of four or five rows, and in some instances attained the high ratio of from ten to fifteen rows. As a rule, the infiltrates were closely packed, with practically no cells escaping into the general parenchyme. This explains the sparsity of lymphoid cells in areas distant from the blood vessels.

The infiltrating cells were predominantly small and medium-sized lymphocytes with many large mononuclears scattered among them. Some of the large mononuclears had phagocytosed lymphocytes and had acquired the size and character of macrophages.

In certain vessels the adventitial coat showed many pigmented polymorphonuclears which, as proved by the large number of those situated in the endothelial wall or near it, had previously emigrated from the blood stream.

In the latter, pigmented polymorphonuclears were extremely numerous, often giving rise to thrombus formations; blood mononuclears partook of the phagocytosis of pigment, as well as the vascular endothelium, leaving a residual quantity of pigment free in the plasma.

The direct hematogenous origin of the vast majority of the lymphoid exudates was clearly evident from the large number of emigrating lymphocytes and monocytes (especially the former). In no other case thus far was the diapedesis of these cells so pronounced and so clear-cut. In this transit through the endothelium these cells assumed varied ameboid protrusions of the nucleus, with advancing cytoplasm of even contour. Mitotic division of lymphoid cells was not often seen. In all instances perithelial connective tissue and the endothelium were cytogenetically inactive.

Extravascular Territory: Foci of glia activity were remarkably few in number and restricted in area. When they occurred, the majority of the cells, though highly ameboid, were still anchored in the general neuroglia "syncytium," the meshes of which showed a few free lymphoid cells (lymphocytes, polyblasts).

Migrating histiocytes and polymorphonuclears were only occasionally seen at a distance from the blood vessels. Extravasation of red corpuscles and petechial hemorrhages were as a rule, not pronounced.

CASE 5.—History.—D. L., a boy, aged 6, admitted to the hospital on July 20, 1925, had complained of pain in the epigastrium three days before. He became drowsy, and the following day his mouth began to twitch, he experienced difficulty in swallowing, and saliva was drooling.

Examination showed rigidity of the neck, right ptosis, palsy of the left side of the face, diminished upper deep reflexes, diminished right knee jerk, lost abdominal reflexes and bilateral Kernig sign. The spinal fluid showed 30 cells per cubic centimeter with 80 per cent lymphocytes. The patient declined rapidly and died three and one-half days after the onset. The clinical diagnosis was polio-encephalomyelitis. The anatomic diagnosis was polio-encephalomyelitis.

Microscopic Examination.—This case differed somewhat from the preceding both in respect to the type of the invading cells and their distribution. The exudates were widely separated, only occasionally being aggregated into groups. The infiltrating cells were predominantly small lymphocytes of surprisingly uniform rotundity and shape, their nuclei showing frequently a conspicuous indentation and lobulation.

Next in abundance were the medium-sized lymphocytes and large mononuclears. Many of the latter were phagocytic, with from one to four lymphocytes engulfed in the protoplasm; others were extremely ameboid, attaining irregular forms.

The infiltration reached an average of two or three rows in the majority of the blood vessels involved and attained in some veins a depth of eight or ten rows. In the latter the large mononuclears, medium-sized lymphocytes and macrophages were most numerous. Polyblasts, only occasionally found in small infiltrations, were likewise more abundant here.

Mitotic division of lymphoid cells was rare. Emigration pictures, though not numerous, were nevertheless of sufficient frequency to warrant the already emphasized contention of the direct hematogenous origin of the majority of the perivascularly situated cells.

Extravascular Territory: The parenchyme was markedly lymphoid, especially near vessels, in which grouping of obviously recently emigrated lymphocytes acquiring a streamlike arrangement gave evidence as to their hemic origin.

Foci of glia activity mobilization were numerous, showing extreme polymorphism of nuclear and cytoplasmic contours in the still fixed cells. Free compound granular cells with characteristic eccentric nuclei and marked vacuolization of cytoplasm were numerous, as were glia cells in the "half differentiated (gitter) condition."

Intermingled with the glia and compound granular cells were lymphocytes, modified and unmodified, histiocytes and occasional polyblasts. In regions adjacent to blood vessels a few lymphocytes differentiated into granular cells were seen.

Extravasation of red corpuscles, rarely extensive, even in the larger infiltrations was either entirely lacking or of meager proportion in the smaller vessels.

Spinal Cord: Perivascular infiltration of the same diffuse nature and of nearly identical morphologic character as in the brain tissue was seen in the cord.

The parenchyme was decidedly less lymphoid and contained areas of glia activation and mobilization, but no well differentiated granular cells.

CASE 6.—*History*.—B. A., a boy, aged 21 months, admitted to the hospital on Nov. 3, 1925, had fallen down a flight of steps two days before, but had appeared perfectly well directly after the fall. The following day, however, he began to vomit, became drowsy and could not hold up his head. The next day he could not stand up and swallowed with difficulty.

Examination showed paralysis of the left side of the face, of the muscles of the neck and of both upper extremities. The biceps and triceps reflexes were not elicited; the abdominal reflexes were absent. There was bilateral Babinski reaction; the spinal fluid contained 115 lymphocytes. He declined rapidly and death occurred from respiratory failure twelve hours after admission. The clinical diagnosis was polio-encephalitis, and the anatomic diagnosis, polio-encephalomyelitis.

Microscopic Examination.—The perivascular infiltration was generalized and of considerable depth, at times attaining from four to six rows. The predominating types of cells were the small and medium-sized lymphocytes with a variable number of large mononuclears and polyblasts. The latter were frequently vacuolated and often showed marked polymorphism of cytoplasmic contours.

The lumina of many vessels were gorged with heavily pigmented polymorphonuclears and large mononuclears. Similarly pigmented types of cells were situated in the adventitial coat; many of them had very likely emigrated together with the lymphocytes. Instances of the latter passing through the endothelial wall were remarkably frequent and clear-cut.

Blood monocytes at times carried the prevailing intravascular pigmentation. Only a few of them were seen in transit. Macrophages with engulfed lymphocytes (from one to four) were frequently seen at the periphery of the adventitial infiltrations.

Mitotic figures were sparse; they were found mainly in the polyblasts.

Extravascular Territory: The parenchyme in all but isolated regions was lymphoid, owing to the presence of many migrating lymphocytes, histiocytes and polyblasts. The hemic origin of the vast majority of these cells was evidenced by the profuse streamlike orientation of lymphoid cells near a number of capillaries and small veins. The presence of groups of scattered lymphocytes at considerable distances from the blood stream suggested that not all the lymphocytes were of direct hemic origin, but were probably proliferation products of pre-existing or previously extravasated lymphocytes.

Many centers of glia activation and mobilization were found especially near the blood vessels, but only in a few instances was a formation of free granular cells noted.

Extravasation of red blood cells was remarkably extensive, the majority of the red blood cells having a habitat beyond the main mass of the perivascular lymphoid exudates.

Spinal Cord: The perivascular infiltration in the spinal cord was similar to that in the brain. The same was true of glia activity and mobilization. Here again formation of free granular cells was but rarely noted.

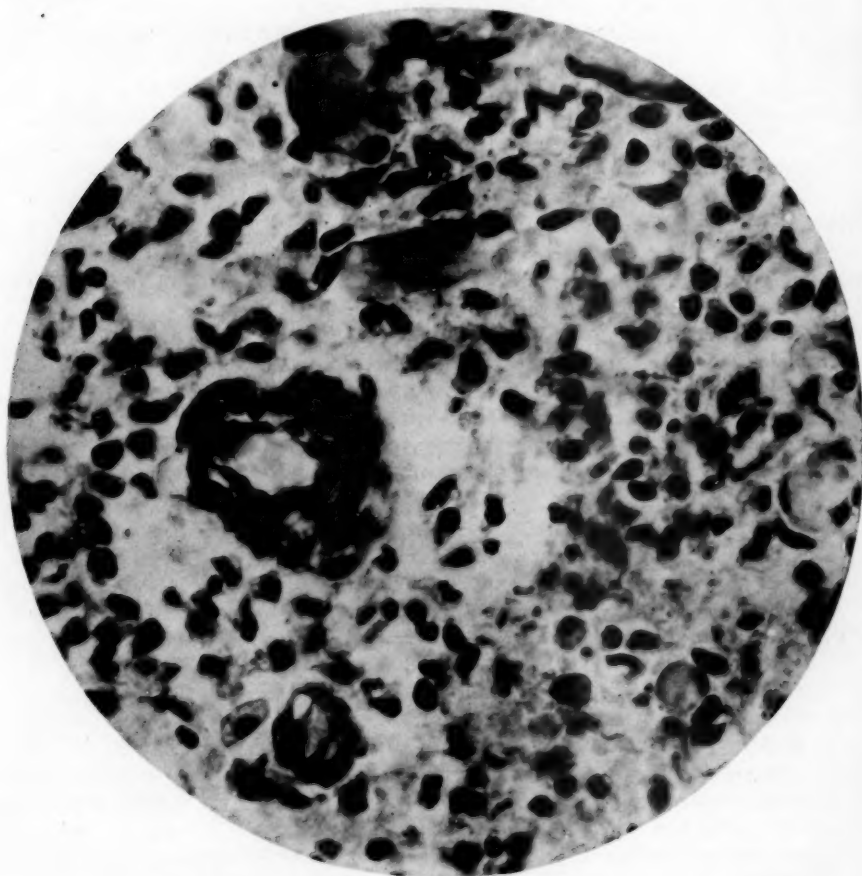


Fig. 21.—Spinal cord. An area of intense glial activity. Among many granular cells are polyblasts, hypertrophying lymphocytes, plasma cells and macrophages; $\times 600$.

CASE 7.—*History*.—L. M., a boy, aged 8, admitted to the hospital on Oct. 29, 1923, had complained of severe headache, lassitude and nausea and vomiting a week before. He returned to school for two days after the onset of the symptoms.

Three days later his temperature rose, and he complained of severe headache. Within twenty-four hours a series of grave symptoms developed rapidly, such as aphonia, dysphagia and difficulty in breathing.

Examination showed nystagmus to the left, weakness of the right central part of the face, immobility of the palate, poor sustaining power in protruding the

tongue, diminished knee jerks, absent ankle jerks. He declined rapidly with the development of a fatal aspiration pneumonia, and death occurred on the eighth day after admission. The clinical diagnosis was polio-encephalitis of the bulbar form, and the anatomic diagnosis was polio-encephalomyelitis.

Microscopic Examination.—In sections of the brain perivascular infiltration was not compressive. When it did occur, it was of small proportion, reaching a maximum of two or three rows, the constituents of which were almost exclusively small and medium-sized lymphocytes with occasional large mononuclears. Types morphologically similar to the latter were observed in the vascular lumen, in which pigmented polymorphonuclears were numerous.

Extravasation of the red corpuscles was only occasionally seen.

Spinal Cord: A somewhat restricted, centrally localized activation of glia cells was found in the cord accompanied by a fairly marked perivascular infiltration. Areas were encountered in which practically all the cells were free granular cells, others in which free lymphoid cells (lymphocytes, large mononuclears, polyblasts) were abundantly intermingled with partially freed glia cells and migrating granular cells. The latter showed a pronounced polymorphism of cell type and frequently simulated typical clasmatoocytes (fig. 21).

The polyblasts with their deeply staining and centrally placed nuclei and variously vacuolated and deeply basic cytoplasm of irregular contour constituted over one half of the free cells in some areas.

That the majority of these polyblasts had originated by way of the blood stream, through emigration and subsequent hypertrophy of lymphoid cells, was clear from the presence of an exceptionally large number (at times from five to ten) rows of lymphocytes and large mononuclears in transit accompanying increase in the size of the cells and the gradual assumption of the morphology of polyblast cells.

Compound granular cells with phagocytic properties and plasm cells (fig. 21) with typical wheel-shaped nuclei and deeply basic and vacuolated cytoplasm were occasionally seen. From the intergrades studied, it would seem that the plasm cells also represented transformed lymphocytes or polyblasts.

Mitotic cell division of lymphoid cells and glia elements were frequently seen.

CASE 8.—History.—M. J., a man, aged 24, admitted to the hospital on Jan. 23, 1920, had become dizzy a week before while at work, developed headache, complained of double vision and soon became drowsy.

Examination showed bilateral ptosis, nystagmus upward and to the right, pupils like pin points, weakness on the left side of the face, diminished power in the extremities and diminished knee jerks.

The patient declined rapidly and died of respiratory paralysis.

The clinical diagnosis was acute epidemic encephalitis, and the anatomic diagnosis, polio-encephalomyelitis.

While the foregoing was the diagnosis during life and apparently substantiated by the early histologic study, it appeared to us that the lesions in the spinal cord associated with objective conditions that indicated involvement of the cord, coupled with the strong similarity of the histologic observations to those in case 1, would justify placing this case with the polio-encephalomyelitis group.

Microscopic Examination.—The perivascular infiltration was pronounced, resembling in degree and morphology of cell type that in case 1, somewhat less marked in the glia activity and the lymphoid invasion of the parenchyme.

The perivascular infiltration consisted of one or two rows about the capillaries, averaged four or five rows for most vessels and attained an occasional maximal depth of from ten to fifteen rows in the larger veins.

As a rule, the exudates were densely packed with small hypertrophying, medium-sized lymphocytes. Mononuclears, often with irregular lobulation and elongation of nucleus, were also present in large numbers, as were polyblasts, which because of their deep basophilia and often strongly vacuolated protoplasm were readily discernible.

Despite a marked increase of local adventitial connective tissue cells and a noticeable frequency of spindle-shaped adventitial cells, a heteroplastic differentiation of lymphoid cells was not observed. Homoplastic formation of lymphocytes and mononuclears, however, was frequent, as was the diapedesis of similar cells through the endothelial lining. Extravasated polymorphonuclears and eosinophils, macrophages and locally differentiated compound granular cells were rare.

Extravascular Territory: The streamlike orientation of migrating lymphoid cells, often of a diffuse and extensive character, was most noticeable in the vicinity of the vessels, especially capillaries, and this accounted for the many migrating lymphocytes and histiocytes found at distances from the vessels.

Glial activity was also quite marked, especially near the capillaries and venules, without extensive differentiation of granular cells, save for isolated individual cells in the perivascular zones.

Extravasation of red corpuscles was not marked.

Spinal Cord: The perivascular infiltration in the spinal cord was similar to and just as intense as that in the brain. The parenchyme, however, was not lymphoid, probably because the exudates were confined to a perivascular habitat.

ACUTE EPIDEMIC ENCEPHALITIS

This group consists of four cases of clinically diagnosed and anatomically verified acute epidemic encephalitis. It is highly significant that, while typical cases of acute epidemic encephalitis can readily be identified and distinguished from the previously described form of acute inflammatory disease of the brain (polio-encephalitis), and that while it is admitted that in typical cases the gross distribution of the lesions differs in these two inflammatory diseases of the central nervous system, the finer histologic features did not present sufficient differences to warrant a clear-cut separation between the two groups.

The same general principles are apparently operative in the histogenesis of the lesions in both groups, as shown by comparing the minute histologic features noted in acute epidemic encephalitis with those of polio-encephalitis.

CASE 9.—History.—P. R., a girl, aged 16, admitted to the hospital on Feb. 4, 1920, had complained of headache and pain in the right side of the jaw eight days before. It subsided at first, but three days later she suddenly became restless and delirious. The day before she was admitted to the hospital she could not void and had to be catheterized.

Physical examination showed that the patient was confused and disoriented. Bilateral weakness of the external rectus muscle, nystagmoid twitchings, bilateral ptosis, tremor of the hands and choreiform movement of both arms were present. The condition progressed rapidly with the appearance of the following signs:

Cog-wheel movement of the eyes, weakness of the right side of the face, disarthria, deviation of the tongue to the left and widespread choreiform

movements. Death occurred on the day following admission. The clinical and anatomic diagnoses were acute epidemic encephalitis.

Microscopic Examination.—The perivascular infiltrations were generalized and of a pronounced character not unlike that seen in case 1. When minimal they reached one or two rows; when maximal, from eight to ten rows. The average depth was three or four rows.

As in the previous case, the cells were predominantly small lymphocytes, and the medium-sized lymphocytes and large mononuclears were next in abundance. The latter were occasionally binucleated, frequently polyblastic, but they did not exhibit phagocytic tendencies in any instance.

Emigrating lymphoid cells were detected in large numbers. Mitosis was less frequently seen.

Extravascular Territory: Frequent profuse streaming of lymphoid cells away from the vessels into the general parenchyme occurred in the extravascular territory. The parenchyme exhibited at intervals centers of glia activity, in which, however, formation of granular cells was not noted.

CASE 10.—History.—R. J., a man, aged 24, admitted to the hospital on Feb. 10, 1920, had developed severe headache and a rise in temperature seven days before. He soon became drowsy and for two days had been unable to open his right eye.

Bilateral ptosis, photophobia, nystagmus, divergent squint, weakness of the face on the left side, rigidity of the neck and cog-wheel movement of the upper extremities were present. The knee jerks were diminished. The patient declined rapidly and died from terminal bronchial pneumonia. The clinical and anatomic diagnoses were acute epidemic encephalitis.

Microscopic Examination.—This case was somewhat unusual because of the marked increase of adventitial connective tissue, which, in spite of its loose stroma-like arrangement, was nevertheless cytogenetically inactive. The infiltration was pronounced (fig. 22). In extent it averaged two or three rows, when minimal and from six to eight rows when maximal in depth.

The majority of the infiltrating cells were small and medium-sized lymphocytes. Hypertrophying lymphocytes and mononuclears were less numerous, some of the latter showing indentation, lobulation and at times entire segmentation of the nuclei. Macrophages with engulfed lymphocytes, erythrocytes, chromatin particles or greenish granules (pigment) were frequently found, constituting the nearly exclusive type of cell around some vessels. Polyblasts were occasionally indistinguishable from adjacent connective tissue cells.

Compound granular cells, partly of hemic origin through transformation of extravasated, hypertrophying lymphoid cells, partly of local neuroglia origin through differentiation, were at times found in the infiltrates. Occasionally the granular cells showed binucleation and phagocytosis.

Polymorphonuclears, rarely of extravascular habitat, were numerous in the lumina of certain vessels, in which groupings of them were occasionally effected through formation of a network of fibrin. Many of the polymorphonuclears were heavily laden with pigment, a varying quantity of which was free in the plasma.

Instances of lymphoid cell migration or mitotic division of such cells (fig. 23) were relatively rare as compared with the other cases considered.

The exudates were relatively fixed in their perivascular habitat, only occasionally tending toward a streamlike orientation and migration of the cells into the general parenchyme.

For the first time conspicuous swelling of the intima in certain vessels was noted.

Extravascular Territory: While extensively lymphoid in areas adjoining blood vessels, the parenchyme distant from the latter contained few migrating lymphocytes and histiocytes. As to the glia cells, groupings in double row formations commonly occurred, with only slight activity in the incipient stage. A few compound granular cells were noted only in the perivascular areas.

Extravasation of red corpuscles with extensive perivascular areas, frequently hemorrhagic, was at times accomplished by complete disintegration of the wall



Fig. 22.—Photomicrograph, showing the degree and the type of perivascular infiltration in encephalitis, as compared with that obtaining in poliomyelitis. Streaming of lymphoid cells is notable; $\times 150$.

of the vessel, leading to a profuse flow of the blood stream into surrounding tissue.

CASE 11.—History.—M. I., a man, aged 21, admitted to the hospital on Jan. 12, 1921, had suddenly begun five days before to experience double vision and complained of headache and pain behind the eyeballs and in the back of the neck. He soon developed twitchings of the upper extremities and of the mouth and suddenly became comatose.

The patient was in a coma and was cyanotic. The pupils were fixed and irregular. All deep reflexes were lost. The spinal fluid contained two lymphocytes per cubic centimeter. The clinical and anatomic diagnoses were acute epidemic encephalitis.

Microscopic Examination.—The perivascular infiltration was fairly marked, averaging two rows for the majority of the vessels involved, and in certain instances attaining a depth of from six to eight rows. In the latter instances the

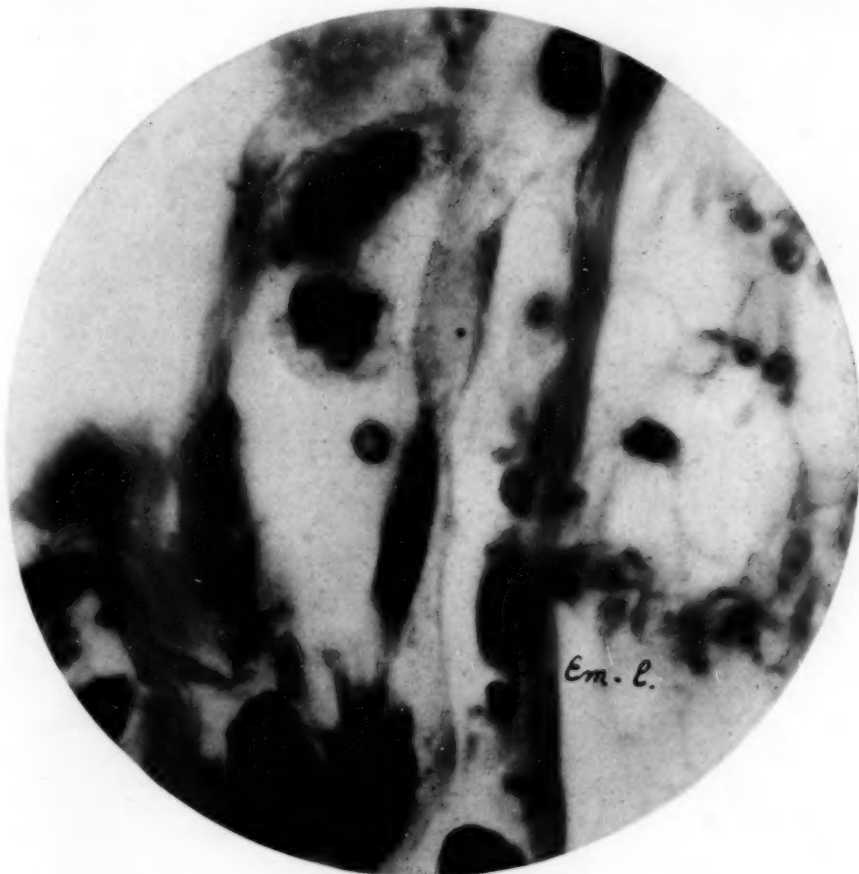


Fig. 23.—Recently emigrated lymphocyte with ameboid process of nucleus (*em. l.*); $\times 2,500$.

majority of the cells were small and medium-sized lymphocytes, with many large mononuclears and polyblasts. The latter showed a deep, basophilic, extensively vacuolated cytoplasm, a vesicular nucleus with deep staining, irregular blocks of chromatin. The cells were highly ameboid, as were also the lymphocytes. In no other case was this phenomenon more pronounced.

Intergrades among the lymphocytes demonstrated that a large number of the perithelial polyblasts had originated through a process of hypertrophy of small

lymphocytes and through emigration of large mononuclears, as shown by the numerous emigration pictures observed.

The polyblasts were occasionally binucleated and frequently underwent division (fig. 24) as did also the large mononuclears, the daughter cells of which were small lymphocytes (fig. 24 *a*).

The perithelial position and the oblong, box-shaped clasmatocyte-like aspect of many of the polyblasts were notable (fig. 24). At times with one side of the cell body in direct contact with the endothelium, and then again touching the endothelium with long pseudopod formations (fig. 24), these polyblasts, at first sight, seemed to originate from the local endothelium through desquamation, but close scrutiny, repeated focusing and study of serial sections revealed in each instance a clear-cut demarcation of the outlines of the cell from the adjacent endothelium.

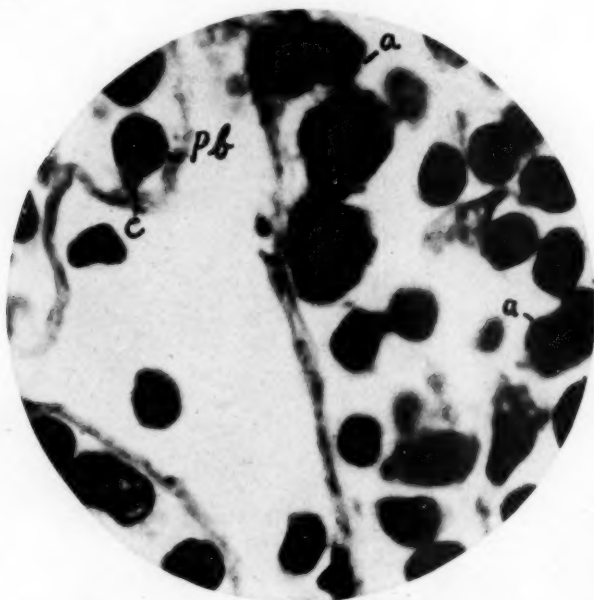


Fig. 24.—Field depicting box-shaped perithelially situated polyblasts (*pb*); one with pseudopod protrusion which touches the endothelium at (*c*), a polyblast in division, with two daughter cells at (*a*); $\times 1,750$.

The prevalent tendency of polyblasts is to skirt the endothelium as elongated or semispherical elements, but frequently they were found at right angles to the endothelial lining. This and the presence of long, irregularly twisted polyblasts indicated the manner in which some of the latter reach a peripheral position in the infiltration.

Polymorphonuclears and large mononuclears laden with pigment were abundant in the lumina of certain blood vessels and were only occasionally encountered beyond the endothelial wall. Macrophages and eosinophils were sparse.

Extravascular Territory: The glia proper was nearly normal, save for regions near blood vessels in which migrating lymphocytes and glia cells in the incipient stage of activity were occasionally noted. Formation of free compound granular cells was but rarely noted, and then only near small capillaries.

Extravasation of red blood cells was general, at times reaching hemorrhagic proportions.

Spinal Cord: Perivascular infiltration and centers of glia activity were almost entirely lacking.

CASE 12.—*History*.—L. K., a man, aged 20, admitted to the hospital on April 4, 1926, had begun to complain of attacks of headache four months before. The attacks occurred repeatedly, varied in intensity, and lasted from four to five hours. During the attacks he would become confused and act queerly. Between attacks there was a feeling of heaviness in his head. There was a vague history of diplopia.

Two days before he came to the hospital he awakened with an intense headache and mental confusion. His conduct became queer, and his head and the left side of his face were "twitching." His memory became somewhat blurred. Aside from slight inequality of the pupils, the right being larger, there were no positive objective signs.

The patient was observed during a similar attack in the hospital. He was confused and uncommunicative. During this attack, which lasted seven hours, he developed an additional objective sign, ptosis of the left eyelid. Shortly afterward divergent squint, nystagmoid twitching, tremor of the hands and cervical tenderness were observed.

On May 2, the patient had another attack resulting in a condition of semistupor. His speech became thick, and paralysis of the right side of the face, hyperactive deep reflexes and Babinski sign on the right side developed.

A rapid decline set in, with an attack of semistupor occurring more frequently, and death took place eleven days after admission to the hospital. The clinical diagnosis was encephalitis of an unusual type. Epilepsy was also considered. The anatomic diagnosis was acute epidemic encephalitis of a hemorrhagic type.

Microscopic Examination.—This case presented a most unusual histologic picture. The perivascular infiltrations were incipient, many of the vessels showing only a few lymphoid elements, which morphologically were mostly small lymphocytes. The maximal infiltrations occasionally reached a seriation of two or three rows of medium-sized lymphocytes and large mononuclears. The latter, which were more abundant, were highly vacuolated and at times pigmented.

Despite the sparsity of exudates, many cells were seen in transit through the endothelium. In certain instances many granules of pigment were present in the endothelium and the adjoining adventitial connective tissue. Such vessels often showed small lymphocytes in pyknosis or in a shrunken condition.

Extravascular Territory: With only isolated migration of lymphoid cells into the general parenchyme, the latter was of course almost free from lymphoid cells, save for a few in regions adjacent to hemorrhages, in which many large mononuclears, lymphocytes, at times even granulocytes had evidently left the main blood flow and were making their way into the general tissue.

In no other case here reported was extravasation of red blood cells so pronounced and generalized as in this. Frequently it was accomplished by a partial or complete disintegration of the wall of the vessel, with the result that the blood stream passed out into the general parenchyme either in a profusely extended oozing fashion or as confined in variously contorted large furrows.

Though centers of glia activity were few, vacuolization about glia nuclei and especially in those about blood vessels was generalized and of a pronounced character.

GENERAL CONSIDERATIONS

The conflicting theories as to the hematogenous or histogenous origin of the free cells appearing in inflammatory areas and in various forms of perivascular infiltrations have already been briefly stated in the introduction. Owing largely to Foot's recent contributions, the pendulum of opinion is seemingly swinging in the direction of the vascular endothelium as the primary factor in the production of these cells. Other workers, notably Marchand and recently Marcora, in overemphasizing the cytogenetic powers and productivity of the local adventitial connective tissue elements, have helped in a large measure to undermine the hematogenous origin of a notable number of these cells. The latter was clearly demonstrated by Maximow nearly twenty-five years ago in his work on aseptic inflammation, and our present study is but a corroboration of his contention.

The detailed descriptions of the histologic observations given in all our cases and particularly in cases 1 and 2 are followed by interpretations which obviate the need of further discussion, and to avoid repetition, we sum up by presenting our conclusions, which follow:

SUMMARY

The vast majority of the infiltration elements in the adventitial spaces, as well as those in the extravascular territory in inflammatory lesions of the central nervous system, particularly in polio-encephalitis and acute epidemic encephalitis, are cells which have filtered out in some selective fashion through endothelial walls of the local blood vessels.

A streamlike orientation and migration of lymphoid cells in the vicinity of the blood vessels and the uniform presence of large numbers of emigrating lymphocytes and large mononuclears, especially the latter, support this thesis. The fact that in some instances (cases 2, 6 and 7) emigration pictures were extremely numerous, while in others (cases 5 and 10) relatively few cells were seen in transit through the endothelial lining, suggests the hypothesis that the cells are extravasated in showers.

The endothelium of the blood vessels does not in a single instance exhibit a cytogenetic activity in the formation of free lymphoid cells through desquamation or mitotic proliferation. This may be regarded as additional proof that the exudates are carried to the site of the inflammation by way of the blood stream from distant hematopoietic organs and tissues.

A notable number of the cells, especially in the larger infiltrations, are probably of local origin, in the sense that they are homoplastic differentiation products of, or previously extravasated, lymphoid cells.

Heteroplastic origin of infiltrating cells from the so-called adventitial cells (small, spindle-shaped, clasmatoocyte-like structures skirting the

wall of the vessel) or from other fixed perivascular connective tissue cells were not observed.

After extravasation the behavior of the lymphoid cells varies. Some remain as lymphocytes (small, medium, large) and large mononuclears; others undergo further differentiation and become transformed into polyblasts, macrophages, granular cells and occasionally into plasma cells, the prevailing differentiation being polyblastic.

The granulocytes, eosinophils and mast leukocytes play practically no rôle in the inflammatory process, since with few exceptions, they are entirely lacking. Polymorphonuclears, however, are usually sparse, though at times they are numerous and in isolated instances constitute the principal cell type among the elements of infiltration.

Extravasation of red blood corpuscles was noted in each case, and while it was generally restricted to the perivascular zone, in many instances it assumed hemorrhagic proportions. The blood stream breaks through a partially disintegrated endothelial lining of a vessel and flows freely into the general parenchyme.

In extravascular territory, centers of glia activity and mobilization are populated by a varying quantity of ameboid lymphocytes, histiocytes and polyblasts constituting the so-called focal areas of infiltrations. Such centers are rich in granular cells derived from the fixed neuroglia.

There are transitional forms of emigrating lymphocytes in their perivascular and extravascular habitat, indicating a "mesodermal" origin for a cell type not unlike the so-called compound granular cell. The latter, in the derivation from lymphocytes, can be traced through the process of cell growth, vacuolization of cytoplasm and displacement of nucleus. The finished product, in common with the granular cells of glial origin, acquires a phagocytic character.

Noteworthy also is the observation that in cases of encephalitis which run an exceedingly stormy course with a sudden and abrupt termination (case 12, fulminating type), the predominant histologic picture is that of numerous hemorrhages and pronounced extravasations of red blood cells with an unusual sparsity of typical small round cell infiltrations. A tentative explanation of this phenomenon may be the fact that the toxic agent reaching the blood vessel is overwhelming in its potency, injuring the blood vessel to such an extent, on the one hand, that only partial, if any, selective filtration of blood elements occurs, and, on the other, that it causes the massive escape of the blood contents to the general parenchyme (Globus and Strauss,¹⁷ 1922).

17. Globus, J. H., and Strauss, I.: Contribution to the Histopathology of Subacute Epidemic Encephalitis, *Arch. Neurol. & Psychiat.* 8:122, 1922.

THE PATHOLOGIC ANATOMY OF PERTUSSIS

WITH ESPECIAL REFERENCE TO PNEUMONIA CAUSED BY THE
PERTUSSIS BACILLUS *

LAWRENCE W. SMITH, M.D.

BOSTON

During the past few years, in the course of the investigative work at the Boston Floating Hospital, about 3,000 cases of whooping cough have been studied from various angles. The summary of the bacteriologic work of the Whooping Cough Commission has been recently published.¹ It is my purpose in this paper to record briefly the pathologic alterations occurring in the eight cases of whooping cough that have come to autopsy in this series.

Since the publication of Mallory's paper in 1913,² nothing has appeared in the literature with specific reference to the pathology of this disease. In his paper, Mallory states that the disease is due to a minute bacillus occurring in large numbers, from dozens to a hundred or more, between the cilia of the epithelial cells lining the trachea and bronchi. He also found the organisms free in the bronchial secretion and enclosed in polymorphonuclear leukocytes, but never within the alveoli of the lungs. For this reason, he concludes that the bronchopneumonia which so often complicates whooping cough seems to be due entirely to other contaminating organisms. He further states that the action of the bacillus is apparently a mechanical one, interfering with the normal action of the cilia and possibly leading to their destruction. This prevents the normal removal of the secretion, resulting in a continuous irritation and the characteristic cough. In addition, there is evidence of the presence of a mild toxin, which is shown in three ways: by the presence of a slight inflammatory exudate, by a lymphocytosis and by the formation of a specific antibody which produces fixation of the complement.

* From the Department of Pathology, the Medical School of Harvard University and the Boston Floating Hospital, aided by a grant from the DeLamar Research Fund.

* Read before the Section on Pathology and Physiology at the Seventy-Eighth Annual Session of the American Medical Association, Washington, D. C., May 19, 1927.

1. Lawson, G. M., and Mueller, M.: *The Bacteriology of Whooping Cough*, J. A. M. A. **89**:275 (July 23) 1927.

2. Mallory, F. B.: *The Pathologic Lesion of Whooping Cough*, Boston M. & S. J. **169**:575, 1913.

In the same year, Rhea³ followed up Mallory's work with some experimental studies on animals, in which he points out the similarity in the clinical and pathologic pictures of pertussis in man, distemper in dogs and shuffles in rabbits. He sounds a note of warning in interpreting experimental results because of the spontaneous occurrence of the latter diseases in the ordinary laboratory animals, noting particularly the similarity in morphology between *Bacillus bronchisepticus** and *Bacillus pertussis*. In this connection, it is interesting to speculate whether these diseases may not represent different reactions to the same organism.

Four years before the publication of Mallory's paper, Wollstein⁴ presented a paper in which he described microscopic sections of the lung in a case of pertussis, which showed bronchopneumonia characterized by marked purulent infiltration with little fibrin. There was a striking necrosis of the exudate, which was covered by masses of bacilli peripherally and which outlined the alveoli. An accompanying bronchitis and peribronchitis, with marked congestion of the capillaries, were present, but few bacilli were found within the vessels.

In respect to the associated clinical pathologic changes, the most frequent references in the literature are to the lymphocytosis. Bourne and Scott,⁵ Heiman,⁶ Craik,⁷ Horowitz,⁸ Seitz⁹ and many others have discussed the relation of the lymphocytosis to the clinical picture, usually from the point of view of diagnosis, although Hess¹⁰ and Cozzolino¹¹ have attempted to explain the mechanism of this peculiar manifestation.

The next most frequent complication is the occurrence of convulsions. These have been variously considered as the result of a definite action of a circulating toxin on the central nervous system (Reiche¹²),

3. Rhea, L.: The Comparative Pathology of the Tracheal and Bronchial Lesions Produced in Man by B. Pertussis and Those Produced in Dogs by B. Bronchisepticus, J. M. Research **32**:471, 1915.

4. Wollstein, M.: The Bordet-Gengou Bacillus of Pertussis, J. Exper. Med. **11**:41, 1909.

5. Bourne, G., and Scott, J. M.: Whooping Cough with a Leucocytosis of 176,000, Brit. M. J. **1**:387, 1922.

6. Heiman, H.: The Clinical Value of Routine Examination of Blood Smears in the Diagnosis of Whooping Cough, Arch. Pediat. **41**:385, 1924.

7. Craik, R.: Whooping Cough and Lymphaemia, Brit. M. J. **2**:344, 1918.

8. Horowitz, J.: Lymphocytosis in Pertussis, Long Island M. J. **7**:275, 1913.

9. Seitz, R. P.: Extreme Leukocytosis in Pertussis: Survey of Literature and Report of Two Cases, Am. J. Dis. Child. **30**:670 (Nov.) 1925.

10. Hess, R.: Lymphocytosis of Pertussis, Ztschr. f. Kinderh. **27**:117, 1920; abstr. J. A. M. A. **76**:1376 (May 14) 1921.

11. Cozzolino, O.: Pathogenic Mechanism of Leukocytosis in Whooping Cough, Pediatrics **32**:761, 1924.

12. Reiche, F.: Convulsions in Whooping Cough, Ztschr. f. Kinderh. **25**:28, 1920; abstr., J. A. M. A. **75**:355 (July 31) 1920.

as the starting up of a latent tetany (Cantilena¹³ and Powes¹⁴), or as a mechanical condition associated with meningeal hemorrhage, comparable to the subcutaneous ecchymoses and conjunctival hemorrhages seen in many cases (Canelli,¹⁵ Lasch¹⁶ and Schick¹⁷). Another unusual complication is that of intussusception, as reported by Condat¹⁸ and Depping.¹⁹

A rare complication of whooping cough is the occurrence of subcutaneous emphysema. This obviously means the rupture of certain of the alveolar walls, with the escape of air into the mediastinum. This extends slowly through the sternal notch and becomes evident by subcutaneous emphysema over the neck and shoulders. In the entire series studied, this has occurred only once with clinical recovery. Stammel²⁰ reported this condition also, and his is the only other reference that I have been able to find, although it is spoken of in most of the clinical textbooks as being a symptom of no great rarity.

The other principal complications are those associated with secondary infections of the upper respiratory tract, particularly the various pneumonias.

In the series studied were eight infants, who came to the hospital with a complicating pneumonia. They were followed carefully, both clinically and bacteriologically, through the remainder of the course of the disease, and cultures were made and blood counts taken either daily or every other day. At autopsy, four of these cases showed a definite diffuse bronchopneumonia, and cultures predominating in pertussis bacilli were obtained from the lungs. In the other cases the pneumococcus, streptococcus or tubercle bacillus were equally important. One of the first four cases ran an atypical prolonged course, and at autopsy showed a marked chronic bronchiectasis and peribronchitis.

13. Cantilena, H.: Whooping Cough and Breast Feeding, *Pediatrics* **31**:555, 1923; abstr., *J. A. M. A.* **81**:1243 (Oct. 6) 1923.

14. Powers, G. F.: Tetany as Cause of Convulsions in Whooping Cough, *Am. J. Dis. Child.* **30**:632 (Nov.) 1925.

15. Canelli, A. F.: Meningeal Hemorrhage as a Complication of Whooping Cough, *Pediatrics* **27**:351, 1919; abstr., *J. A. M. A.* **73**:303 (July 26) 1919.

16. Lasch, W.: The Pathogenesis of Hemorrhage in Whooping Cough, *Monatschr. f. Kinderh.* **28**:441, 1924; abstr., *J. A. M. A.* **83**:1115 (Oct. 4) 1924.

17. Schick, B.: Konfluente Hautblutungen im Gesichte bei Pertussisartigen Hustenauffällen, *Mitt. d. Gessellsch. f. inn. Med. u. Kinderh.* **12**:98, 1913.

18. Condat: Invagination intestinale au cours d'une coqueluche, *Arch. de méd. d. enf.* **17**:207, 1914.

19. Depping, C. W.: Two Cases of Intussusception Following Whooping Cough, *U. S. Naval M. Bull.* **10**:319, 1916.

20. Stammel, C. A., Jr.: General Cutaneous Emphysema in Whooping Cough, *Lancet-Clinic* **111**:442, 1914.

Siegenbeek van Heukelorn²¹ reported similar fibrotic changes in two cases in adults. It is interesting to note that the same process may occur even in children. Figure 3, illustrating one of our cases, shows the extensive change of the epithelium from the usual columnar ciliated form to a squamous type.

REPORT OF REPRESENTATIVE CASES

CASE 1.—*History*.—A girl, aged 15 months, was admitted to the hospital with a history of having had several convulsions in the preceding twenty-four hours.

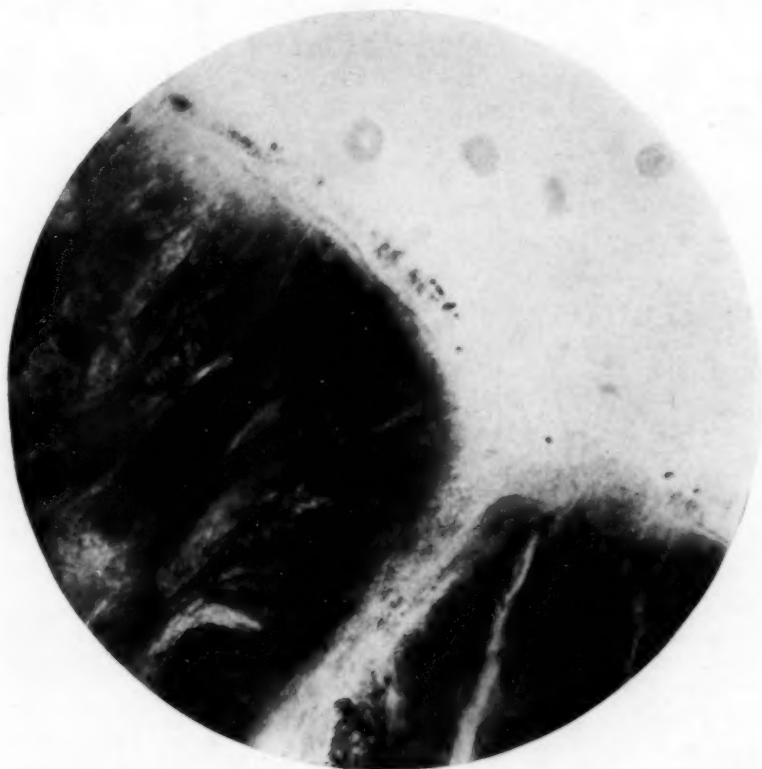


Fig. 1.—Appearance of primary bronchus, showing clumps of bacteria enmeshed in cilia of epithelium. High power. Approx. 1,000 \times Leitz 2 mm. and no. 4 ocular.

It was suspected that this condition was due to intracranial hemorrhage. The infant was in a coma. Following radiation, she improved somewhat temporarily, but during the next twenty-four hours failed progressively, dying thirty-six hours after admission.

21. Siegenbeek van Heukelorn, J.: Changes in the Lungs Following Whooping Cough, *Nederl. Tijdschr. v. Geneesk.* 2:855, 1920.

Autopsy.—The body was that of a normal appearing infant about 14 months of age. Slight edema was present in the lower eyelids. There was moderate dilatation of the heart. No other pathologic lesions were found except in relation to the chest. A diffuse bronchopneumonia involved both lungs, but it was more marked in the right superior lobe and in the left inferior lobe. Here, there was definite patchy consolidation with a grayish, dry cut surface. The rest of the lungs were edematous and markedly congested.

There was a concomitant hyperplasia of the tracheobronchial lymph nodes with lymphadenitis. The trachea and bronchi were pale and edematous, with a few

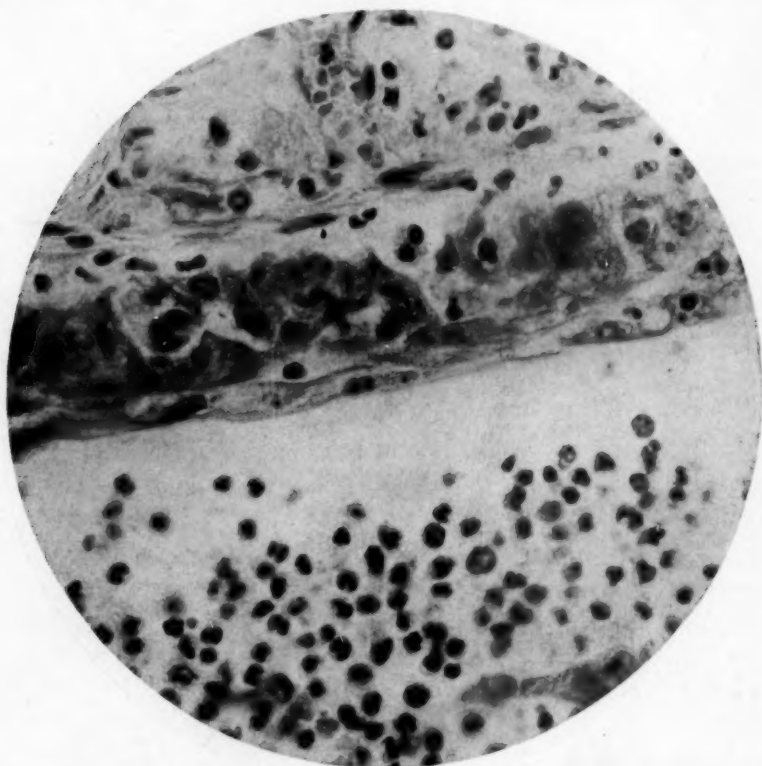


Fig. 2.—Appearance of bronchial mucosa, showing early progressive changes in epithelium in the development of bronchiectasis, emphasizing the beginning tendency toward formation of squamous cells. Leitz 4 mm. obj. no. 2 ocular.

submucous petechial hemorrhages. There was a marked increase in the secretion of mucus.

Histologically, a diffuse bronchopneumonia with a mucopurulent exudate showing relatively little fibrin was present. There was marked desquamation of the alveolar epithelium with an accompanying lymphocytic infiltration of the peribronchial tissues and the alveolar walls. This mononuclear reaction was also found within the alveoli. The most striking lesion was the presence of myriads of minute coccobacilli which presented the morphologic characteristics of the pertussis bacillus. The reaction to this organism was one of an exudative and

proliferative character. There was little evidence of any severe toxic necrosis. The lesion was apparently a direct extension from the bronchi, which appeared similarly infested by bacteria. The lymph nodes were hyperplastic and showed marked infiltration by mononuclear phagocytic cells.

ATYPICAL CASES WITH COMPLICATIONS

CASE 2.—History.—A girl, aged 3, was admitted to the hospital with a diffuse bronchopneumonia in both lungs, with a temperature ranging from 98.6 to 104.8. The pulmonary lesions increased in severity and by roentgen-ray examination the diagnosis of miliary tuberculosis was suggested. Terminally, there was definite evidence of beginning meningeal involvement.

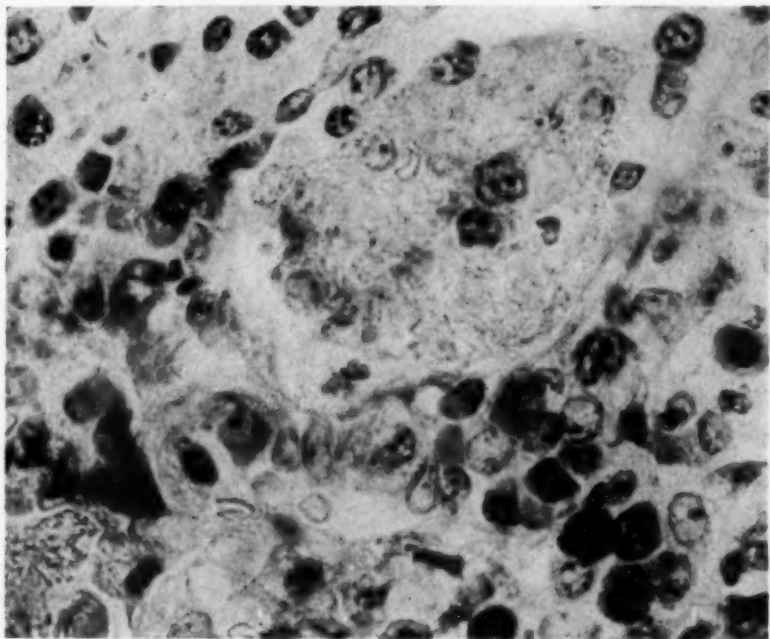


Fig. 3.—This illustration emphasizes the characteristic lymphocytic infiltration of the alveolar walls, and the part played by the lymphocytes in the actual alveolar exudate. The bacilli in the meshes of the fibrin of the exudate should be noted. High power. Leitz 2 mm. oil obj. no. 2 ocular.

Autopsy.—The body of the child was fairly well developed, though somewhat underweight. The pathologic alteration was that of a diffuse miliary tuberculosis involving all the viscera. The lungs showed a diffuse gelatinous bronchopneumonia, as well as the more focal miliary lesions. The mediastinal lymph nodes presented evidence of a long standing caseous tuberculosis, which showed a good deal of fibrosis peripherally.

Histologic examination confirmed the gross picture. In addition, a fairly characteristic mucopurulent catarrhal bronchitis and bronchiolitis were present. No pertussis bacilli were seen.

Comment.—This is the only case in the series in which a definite relationship between tuberculosis and whooping cough has been found. It apparently represents a "lighting up" of a hilum tuberculosis as a result of the superimposed pertussis.

CASE 3.—History.—A boy, aged 8 months, was admitted to the hospital in the spasmodic period of the disease, with a complicating diffuse bronchopneumonia. He had been ill about a month. During the week in the hospital, the pneumonic process increased in area, and the child progressively failed.



Fig. 4.—Appearance of lung in case 3, illustrating the extraordinary and interstitial fibrosis.

Autopsy.—The body was that of a well developed and well nourished infant who appeared about 6 months of age. Pathologic alterations were not noted except in relation to the cavity in the chest. A marked pneumonic process involved the right lower lobe especially. It extended generally, however, throughout the rest of both lungs. It presented certain unusual features in that it appeared to be a chronic organizing process with relatively little evidence of any acute inflammatory reaction. The lungs were grayish red, firm and almost lobulated as a result of fibrosis. The bronchi and trachea showed moderate catarrhal inflammatory changes with considerable edema and some slight injection. The mediastinal lymph nodes presented a compensatory subacute lymphadenitis.

Microscopic Examination.—Sections through the lungs presented a diffuse catarrhal bronchitis, bronchiolitis and bronchopneumonia. There was evidence of marked fibrous organization of the tissue of the lungs. A beginning formation of bronchiectatic abscesses was present, with a pseudometaplasia of the lining alveolar epithelium of the cuboidal and squamous type. Extensive lymphocytic infiltration of the peribronchial tissues and of the alveolar walls was seen, with many lymphocytes in the alveolar exudate. Cultures taken showed a pure growth of pertussis bacilli.

From the accumulated data of the 3,000 cases, certain general conclusions in respect to the changes in the lungs seem justifiable. Nearly 10,000 roentgenograms were taken during the course of the disease. Some of the symptoms were so constant as to have been of value diagnostically. The fine differences between a lung affected by whooping cough and one involved in some other form of bronchitis are sufficient usually to make such a differential diagnosis. As noted previously, the cases (Bowditch, Leonard and Smith²²) have been grouped in three main divisions for purposes of tabulation: those showing the earliest recognizable changes, those showing the typical picture and those complicated by secondary bronchopneumonia. In approximately 80 per cent of the cases, it is safe to say that there is a demonstrable peribronchial thickening involving chiefly the lower branches of the bronchial tree. For a long time I have been curious as to the exact histologic picture associated with this roentgenologic manifestation. In the cases presented here, the peribronchial lymphoid hyperplasia seemed sufficient to explain the change. In addition, an accompanying edema and some fibrosis usually were present. During the course of the disease, even within a matter of a week or ten days in many cases, there was demonstrable diminution in this peribronchial shadow, as shown by the roentgen ray. It is difficult to say with any degree of assurance that the patients who have been treated by the roentgen ray show this change more rapidly than the others, but it is my impression that this is so.

Concomitant with the peribronchial thickening is an enlargement of the tracheobronchial lymph nodes. This observation also was confirmed in the fatal cases herewith presented. Microscopically, an extraordinary lymphoid hyperplasia and mononuclear phagocytosis are seen. Such a manifestation was indicated also by Goubau,²³ who similarly comments on the hyperplasia of the tracheobronchial lymph nodes. Ruckle²⁴

22. Bowditch, H. I.; Leonard, R. D., and Smith, L. W.: Studies on the Roentgen-Ray Treatment of Whooping Cough, *Am. J. Dis. Child.* **28**:322 (Sept.) 1924; Smith et al.: Treatment of Pertussis by Roentgen Ray, *J. A. M. A.* **85**:171 (July 18) 1925.

23. Goubau, F.: l'Adenopathie tracheo-bronchique simple, suite de coqueluche, *Belgique med.* **20**:327, 1913.

24. Ruckle, W. M.: Enlargement of Lingual Tonsil in Whooping Cough, Correspondence, *J. A. M. A.* **69**:2139 (Dec. 22) 1917.

observed the generalized lymphoid hyperplasia in pertussis, noting particularly the frequency with which the lingual tonsil is involved.

This hyperplasia of the lymph nodes also is diminished as shown by the roentgen ray, some change usually being demonstrable within two or three weeks, although the complete reversion to normal often is delayed for many weeks or even months. In a few instances, permanent enlargement of the glands with fibrosis is seen after as long a period as three years. One difficult quantitative estimate in these cases is the securing of a normal roentgenogram of the chest before the onset of the disease. We have been fortunate in doing this in approximately 300 cases, and our observations support the general conclusions stated.

In respect to otitis media, no published reports seem to be available. It is difficult, perhaps, to estimate quantitatively the relationship between the occurrence of this condition, either unilaterally or bilaterally, to the disease itself, as otitis media is such a frequent complication of any infection of the upper respiratory tract. It is interesting to note that in this extensive series of cases, the involvement of either or of both middle ears has been of relatively infrequent occurrence, only 103 cases having been found. In one of the cases, cultures were made to determine the infectious agent, and the pertussis bacillus was isolated repeatedly in practically pure culture. From that time, cultures were made as a routine from all the cases of otitis media in order to determine whether this organism was present, but the results were negative. From a theoretical standpoint, it seems surprising that in a disease characterized as this one is by tremendous paroxysmal coughing, with the direct anatomic relationship of the eustachian tubes to the posterior nasopharynx, the ears should not become infected more frequently.

When one reviews the literature of the outstanding pathologic alteration associated with pertussis, it is apparent that the importance of the pertussis bacillus itself as the principal cause of many of the secondary complications, especially bronchopneumonia, has not been sufficiently recognized. These few cases illustrate this fact, as in seven of eight fatal cases of whooping cough the pertussis bacillus was recovered culturally from the lungs and demonstrated histologically, and apparently it was the predominating etiologic agent in four of them.

If in this paper I have shown the importance of the pertussis bacillus as a primary cause of death in infants, its purpose will have been accomplished.

SUMMARY AND CONCLUSIONS

A general review of the pathologic alterations in whooping cough is presented. This includes a consideration of both the common and the more unusual complications: the lymphocytosis, the peribronchial thickening, the enlargement of the tracheobronchial lymph nodes, the

occurrence of meningeal, conjunctival and other hemorrhages and the rare incidence of subcutaneous emphysema, intussusception and otitis media, caused by the pertussis bacillus.

In addition, a more detailed study of the cases coming to autopsy, with a complicating bronchopneumonia, is presented. In this study are discussed the extensive changes in the lung which may be associated with pertussis and infection by bacilli; as observed pathologically these infections include bronchiectasis, fibrosis and even a pseudometaplasia of the bronchial epithelium from the columnar to the squamous type. An attempt has been made to emphasize the importance of the organism as a primary etiologic factor in the mortality rate.

DISCUSSION

DR. MARTHA WOLLSTEIN, New York: It is a curious fact that while pertussis occurs in all countries, involves all ages and causes so large a percentage of deaths in young children, the literature is notably lacking, as Dr. Smith has said, in accounts of the pathologic histology of the disease. Even Dr. Mallory's paper describing what is apparently the essential, if not the specific, lesion of the disease did not stimulate the study of the minute pathologic changes; consequently, Dr. Smith deserves a great deal of credit for having cleared up a question that has hung fire so long. I have been able to study only two cases of pertussis with bronchopneumonia which came to autopsy. In both, pertussis bacilli were cultivated in large numbers from the lungs, but pneumococci were present as well. I thought that I was able to demonstrate the pertussis bacilli in the alveolar exudate, and the reason Dr. Mallory could not confirm that observation was probably because the three patients that he describes in his paper were seen early, before the development of the alveolar exudate that was present in my first case.

The second case occurred several years later. I had no difficulty in demonstrating the lesion of the bacilli entangled in the cilia and then their presence in the alveolar exudate. There was also what I interpreted as a necrosis occurring early in the exudate. I attributed that to the action of the endotoxin which Bordet and Gengou described as produced by their bacillus and with which they were able to produce mild necrotic lesions in rabbits.

The lymph nodes in both my cases showed the extensive enlargement that Dr. Smith described, and both patients died in the first week of the pneumonia and in the second week of the spasmodic stage of the pertussis. The lungs grossly were not firm, the pneumonic lesion was still in an early stage, and it was distributed over both lungs in practically all the lobes. The congestion and the edema were marked features, however.

DR. W. H. PARK, New York: I disagree with Dr. Smith only in the use of words. He said that active immunity did not develop through whooping cough. One might just as well say that active immunity did not develop through vaccination against smallpox, because a few years after vaccination some persons will develop smallpox after exposure, and after twenty years, many will develop the disease. I do not think any one knows of any case of a patient developing a second attack of whooping cough within a few months.

All physicians know that if they use a selected medium they are more apt to get a nearly pure culture of the germ that the mediums suit. I am always skeptical of obtaining a pure culture of any microbe in a case of bronchopneu-

monia, and I wondered whether Dr. Smith used a medium especially selected for the growth of the whooping cough bacilli or whether he used several different mediums suitable for other organisms as well.

DR. J. A. KOLMER, Philadelphia: This paper carried my recollection back about nineteen years to the time when it was thought that a differential blood count would be of diagnostic value in whooping cough because of the sudden increase in small lymphocytes, and the changes in the lymphoid tissues reported may bear a relation to this change in the blood. I am also under the impression that whooping cough is most infectious during the catarrhal stage, but as the bacilli have been demonstrated in these cases of bronchopneumonia, I am wondering whether this clinical impression is really borne out in fact.

I should also like to ask Dr. Smith whether in his cases an investigation was made of the upper respiratory tract to determine whether the Bordet bacillus was present there as well as in the pneumonic lesions?

DR. SMITH: I accept Dr. Park's amendment in respect to the immunity conferred. I meant permanent rather than active.

As far as the mediums are concerned, one almost has to use a selective medium to isolate the pertussis bacillus. However, I utilize regularly control cultures on chocolate mediums and the ordinary blood agar. In three of the four cases in which cultures of pertussis bacillus were secured, no growth was obtained from the other mediums. In the fourth case, an influenza bacillus also was present. That has been the great difficulty in the differential diagnosis at all times, and that is why it is necessary to resort so definitely to selective mediums.

In respect to the value of the lymphocytosis in whooping cough, it has been found now in a large proportion of cases that there is a definite rise, the average figure for the whole group being between 12,000 and 15,000 by the end of the first week of the catarrhal stage of the disease. From the bacteriologic studies that have been carried out and that are being published separately at the present time, it has been found that for purposes of practical public health the infectious period of whooping cough is almost invariably within a period of thirty days. Furthermore, it may be considered as existing for three weeks from the beginning of the paroxysmal stage. Ordinarily, the disease is most infectious during the second week of the catarrhal stage and during the first week of the paroxysmal stage. I might say that in the pneumonias reported in this paper all the patients died within the first week of the onset of the pneumonia, so that death occurred well within the first three weeks of the disease and thus at the height of the infectious period.

GASTRO-INTESTINAL LYMPHOGRANULOMATOSIS*

HELEN C. HAYDEN, M.D.

AND

CARL W. APFELBACH, M.D.

CHICAGO

Unusual anatomic and clinical forms of lymphogranulomatosis have been studied with increasing frequency during the last decade, especially localized and acute types. The gastro-intestinal variety has become important because of many failures to recognize it either during life or from its gross anatomic features.

Studies of gastro-intestinal lymphogranulomatosis progressively increased after 1913, when Schlagenhauser (1913) described gastric lymphogranuloma without involvement of other organs. Later studies, the majority in the European medical literature, give credit to Schlagenhauser for directing particular attention to the gastro-intestinal form. Also, in discussions of the localized gastro-intestinal form of this disease, many of the treatises (Simonds, Sternberg, Longcope, Bunting) on lymphogranulomatosis include chiefly studies made after 1910. Ziegler, in 1911, included an intestinal type in his clinical classification of Hodgkin's disease, but based his conception chiefly on the cases cited by Wells and Maver, Symmers, Hoffmann, Butterfield and Stoerk. Some of the latter cases (Wells and Maver, Symmers and Stoerk) in recent years have not been included with lymphogranulomatosis in some of the reviews mentioned, and are described by Ewing and by Biggs and Elliott as a distinct entity among the diseases associated with excess of lymphoid tissue, namely, pseudoleukemia gastro-intestinalis, characterized by hyperplasia of lymphoid tissue in the wall of the gastro-intestinal tract. Wells and Maver collected eight reports from the literature, described one case and employed the name pseudoleukemia gastro-intestinalis, "a division of the general group of cases that presents the anatomical and symptom-complex of Hodgkin's disease."

Obviously, there are several reasons for the recent recognition of a localized form of gastro-intestinal lymphogranulomatosis. First, the gross alterations in the gastro-intestinal tract in leukemia, pseudoleukemia, lymphosarcoma and lymphogranulomatosis are similar in that each one may occur as a more or less diffuse thick infiltration of the wall of the gastro-intestinal tract, the new tissue having the gray, homogeneous, translucent character of adenoid tissue, and ulceration of

*From the Pathological Laboratories of The Presbyterian Hospital and The Norman Bridge Pathological Laboratory of Rush Medical College of the University of Chicago.

the mucous membrane occurs frequently and early in all. Second, only in recent years have the many synonyms of lymphogranulomatosis or Hodgkin's disease become obsolete. With the decrease in synonyms, the histologic characteristics of lymphogranulomatosis have become better differentiated, and, therefore, the recognition of the various lymphomatoses has become more exact. Third, Terplan (1922) and others believe that previous to 1913, the localized form of lymphogranulomatosis was frequently classified as sarcoma of the bowel or tuberculous enteritis. In favor of this explanation is the failure, noted in many recent reports, to recognize lymphogranulomatosis grossly when the postmortem examinations were made, sarcoma, lymphosarcoma or hyperplastic tuberculosis having been frequently diagnosed.

Lymphogranulomatosis now occupies a position in clinical medicine and morbid anatomy similar, in many respects, to that of syphilis and tuberculosis previous to the discovery of *Spirochaeta pallidum* and *Bacillus tuberculosis*. It embraces many clinical and anatomic groups united mainly by common histologic changes, and one knows from the early history of syphilis and tuberculosis that the classification of unusual forms of these granulomas was difficult and deceptive when based on histologic characteristics alone. The difference of opinion among pathologic anatomists in regard to the anatomic classification of lymphogranulomatosis proves that the histologic interpretation of this disease is also deceptive. Whereas the majority classify it as a non-specific infectious granuloma, Lichtenstein, Fraenkel and Much, and Sternberg believe that it is a variety of tuberculosis, and Warthin, Mallory and Levin group it with the neoplasms. Lubarsch states that "lymphogranulomatosis like other lymphomatoses occupies an intermediate position between chronic generalized infectious diseases and blastomas." The inclusion of the localized forms in the general group of lymphogranulomatosis, however, does not rest solely on the histologic characteristics. The extent and location of the gross alterations in the gastro-intestinal form, as described in the table, reveal a progression in degree from the localized to the more characteristic generalized type.

The histologic alterations of the localized forms should mirror the typical microscopic anatomy of generalized lymphogranulomatosis so that the inclusion of the unusual varieties may not further complicate the conceptions of this disease, as the histologic alterations that may occur in acute and chronic generalized lymphogranulomatosis are variable, and recognition of the unusual types is sometimes difficult. The typical histologic anatomy of lymphogranulomatosis accepted by most writers, the standard by which the localized forms have been recognized, has the following characteristics: the granulation tissue occurring chiefly in lymphadenoid structures, is usually more uniform and diffuse than that of the specific granulomas; the polycellular character is pronounced;

eosinophilic leukocytes and plasma cells are more common than in other granulomas; the giant cell with a vesicular nucleus and the multinuclear giant cell, described by Sternberg and Reed, are not found in such large numbers in other granulation tissue.

The search for etiologic factors in the localized forms has, of course, followed the recent trend of conceptions associated with the generalized type, especially concerning the relation of tuberculosis to this disease. Fraenkel-Much granules were demonstrated by Eberstadt in his case. Tubercle and diphtheroid bacilli, amebas (Kofoid, Boyers and Swezy), thallophytes (Merk) and mycelia-like bodies (Kuczynski and Hauck) have been described in lymphogranulomatosis, but not in the gastro-intestinal form.

Gastro-intestinal lymphogranulomatosis is not a sharply circumscribed anatomic form of this disease. The location and extent of the lymphogranulomatous infiltrations described in the recent studies of the gastro-intestinal form, and reproduced in the table, illustrate that various degrees of infiltration of the gastro-intestinal tract and internal organs may occur. There are instances in which there is a single tumor of the bowel, and others with extensive and multiple ulcers of the gastro-intestinal tract alone, or associated with enlargement of several groups of lymph glands. In most of these cases, however, the only symptoms observed were confined to the gastro-intestinal tract. There were not any large superficial lymph glands or extensive infiltrations of the liver or spleen.

We have rather arbitrarily selected the reports of twenty-six examples of lymphogranulomatosis of the stomach and intestine to illustrate the characteristics of this disease. Although we endeavored to make the selection with care, others will presumably call attention to omissions or object to some cases we have included. A selection is not easily made because of the slow emergence of the disease as an entity from a great variety of conditions in which lymphoid tissue is produced to excess.

Of the twenty-six recent reports of gastro-intestinal lymphogranulomatosis, the alterations studied in three bodies were in the stomach, in ten in the small bowel, in ten in the stomach, small and large bowel, and in three in the large bowel. Some authors have objected to the inclusion of the cases of de Groot, Catsaras and Georgontas, and de Jong in the localized form, because the extent of the disease was determined only by surgical laparotomy. Their cases clinically were diseases of the gastro-intestinal tract, and the physical signs of generalized lymphogranulomatosis were not present.

We will describe three instances of this disease, in two of which there were chiefly gastric manifestations during life, and the disease was localized to the stomach, the regional lymph glands and slight

Clinical and Anatomic Manifestations of Twenty-Six Recent Studies of Gastro-Intestinal Lymphogranulomatosis Collected from the Medical Literature

Case Number, Author and Date	Age and Sex	Duration of Symptoms	Clinical Diagnosis	Clinical Manifestations	Temperature	Morphologic Blood Examination	Part of Gastro-Intestinal Tract Involved	Types of Gross Change in the Gastro-Intestinal Tract	Lymph Glands Involved	Other Organs Involved	Associated Pathologic Changes	Cause of Death
1. Steindl, 1924	Not given; F	Severe, 2 mo.; mild, 1 yr.	Cardioma of stomach	Indefinite distress in left upper quadrant; eructations; anorexia; occasionally vomiting; filling defect of pyloric end in roentgenogram	No fever	Red blood cells, 3,680,000; white cells, 8,910; N., 72; L., 13; E., 3	Pyloric end of stomach	Diffuse thickening of inner surface of irregular and ulcerative	Regional along greater and lesser curvatures	None found at laparotomy	None	Patient recovered
2. Scott and For- man, 1916	53; M	More than 1 yr.	Gastric carcinoma (malignant lymphoblastoma following operation)	Pain in the upper abdominal quadrants; tenderness in epigastrium; occult blood in stools; no free and no lactic acid in stomach contents	Intermittent between 99 and 100.6 F.	White cells, 7,800; N., 70; L., 24; T., 2; E., 4	Stomach to pylorus	Irregular infiltration of mucosa; shallow ulcers	Inguinal; perigastric at lesser curvature	From 3 to 5 cm. of esophagus adherent to uterus	Necrosis of the upper third of the spleen	Not specifically stated (2 days after laparotomy)
3. Heilmann-Hatry, 1923	52; F	Several weeks	Intestinal neoplasm	Severe abdominal pain and diarrhea at onset; palpable mass; blood in all stools; onset sudden and resembling bowel obstruction	Continuous terminally, 39 C.	Marked secondary anemia; leukopenia; N., 70; L., 29	Junction of ileum and jejunum	Single large ulcer	Regional in the mesentery	Ulcerated portion of small bowel adherent to uterus	Marked anemia; old apical tuberculous	Not specifically stated
4. Catsaras and Georgotas, 1914	34; M	1 year	Bowel obstruction	Cramplike abdominal pain; constipation alternating with diarrhea; palpable tumor in ileocecal region	Not mentioned	Not mentioned	Ileocecal valve	Single large nodule producing bowel obstruction	None	Unknown; specimen from laparotomy	None	Unknown; occurred 4 mo. after operation; no necropsy
5. De Groot, 1921 (case 1)	69; M	About 7 mo.	Tumor in ileum	Vomiting; anorexia; abdominal pain; constipation; marked gastric retention with long bacilli	Not mentioned	Not mentioned	Jejunum	Tumor in jejunum almost obliterating lumen; ulceration of surface	None mentioned	None mentioned; operative specimen	None	Recovery following removal of tumor; eventual outcome unknown
6. Pamperl and Terplan, 1925	38; M	Mild, 2 yr.; severe, 1 mo.	Stenosis of ileum	Onset with pain in left upper quadrant and diarrhea; later symptoms of bowel obstruction; occult blood in stools	No fever	Not mentioned	Distal part of ileum	Single mass in ileum leading to intussusception at the ileocecal valve	Regional in mesentery	None found	Bronchiectasis	Recovery following resection of mass in ileum
7. Eberstadt, 1914	57; M	About 1 year	Cardioma- stenosis of colon; later, gastric carcinoma	Abdominal pain; diarrhea alternating with constipation; small defect at pyloric end; free acid 39; total 52	Not mentioned	Not mentioned	Duodenum; jejunum	Circular ulcer in duodenum and jejunum; small ulcers throughout small bowel	Mesenteric	None found	None	Peritonitis following resection of tumor in jejunum
8. Partsch, 1921	39; M	6 mo.	Not mentioned	Diarrhea early; anorexia; vomiting; no free acid in stomach contents	Irregular, reaching 38 C.	Not mentioned	Duodenum; jejunum	Nodules and ulcers	Mesenteric	None found	None	Unknown
9. Lupu and Cra- elum, 1924	20; M	6 wk.	Not mentioned	Epigastric pain; purpura of abdominal wall; no melena	Not mentioned	Leukocytosis	Small intestine; ileocecal valve; ascending colon	12 sessile tumors in small intestine; mass in ileum and ascending colon	Periaortic, forming mass 5 by 2 by 2 cm.	Pancreas infiltrated	None	Not specifically stated

N. indicates neutrophilic polymorphonuclear leukocytes; L., lymphocytes; M., monocytes; T., transitional, and E., eosinophils.

10. Warfield and Krieger, 1918	27; M	9 mo.	Pulmonary and dry, recent tuberculous	Intermittent abdominal pain alternating; vomiting; distention of abdomen below umbilicus; constant diarrhea	Not mentioned	White cells, 7,000; S, 66; L, 33; T, 6	Small and large intestine	Nodules with uniform thickening of wall; perforation of jejunal ulcer	Mesenteric	Spleen	Emaciation	Acute generalized peritonitis
11. McAlpin and von Glahn, 1922	22; F	6 yr.	Hodgkin's disease (biopsy of mesenteric gland)	Abdominal pain; anorexia; obstinate vomiting; occasional vomiting; mass in the right lower quadrant; mass from ensiform to umbilicus; decrease in size of masses following roentgen ray	Intermittent early; remittent late	Leukocytosis early; leukopenia late	Colon at the splenic flexure; distal half of the transverse colon	Thickening of splenic flexure with nodules in the serosa; ulcers and perforation of the transverse colon	Mesenteric; ileac; pelvic; perigastric; mediastinal	Spleen; peritoneum; liver; pleura	Left hydrothorax	Acute generalized peritonitis
12. De Groot, 1921 (case 2)	49; M	1 year	Not mentioned	Gastric disturbance; signs of pyloric obstruction; no free acid and no lactic acid in stomach contents	Not mentioned	Not mentioned	Stomach and jejunum	Nodule and two ulcers in stomach; two regions of stenosis in jejunum	Mesenteric	None found	None	Not mentioned
13. Terplan and Wallesch, 1923	58; M	4 mo.	Gastric ulcer or carcinoma	Marked abdominal distress; anorexia; eructation; defect in lesser curvature; evidence of pyloric stenosis	Not mentioned	Not mentioned	Stomach; duodenum; jejunum	Ulcers in stomach; infiltration and ulcers in duodenum and jejunum	Mesenteric; peripancreatic	None	Old tuberculous of lung and mesenteric lymph glands	Not specifically stated (followed gastroenteroscopy)
14. Schlagenhauser, 1920 (case 2)	44; M	From 2 to 3 mo.	Anemia and gastric ulcer	Abdominal pain; moderate distention of abdomen; blood in stools	No fever	Not given	Stomach; duodenum; ileum	Multiple small ulcers and infiltrations	Small left axillary; mesenteric	Pharynx; lung; spleen; myocardium	Old tuberculous of gastro-intestinal lymph glands	Anemia from gastro-intestinal hemorrhage
15. Kaznelson, 1924	58; M	Several years	Gastric ulcer	Diarrhea early; abdominal pain; anorexia; eructations; no palpable tumor; defect in lesser curvature at pylorus; blood in stool; free acidity 8, total 26	38.8 C. for ten days	Not mentioned	Stomach; duodenum; small bowel	Multiple small ulcers	Regional in mesentery; periaortic	None	Tuberculous of periaortic and mesenteric lymph glands	Not specifically stated
16. Novotny, 1923	56; M	10 mo.	Gastric ulcer (carcinoma of sigmoid following laparotomy)	Abdominal pain; diarrhea; vomiting; anorexia; loss of weight; epigastric tenderness; blood in stools; no free acid, total 29; lactic acid present in stomach contents	No fever	Not mentioned	Stomach; duodenum; small bowel; sigmoid colon	Nodules and ulcers in stomach, duodenum, jejunum and ileum; perforation of four jejunal ulcers; single ulcer in sigmoid colon	Peripancreatic; mesenteric	None	Peritonitis	Peritonitis
17. Schlagenhauser, 1920 (case 1)	47; M	Few weeks	Gastric and intestinal ulcers (tuberculous?)	Abdominal pain; constipation followed by diarrhea; anorexia; distention of abdomen	Intermittent between 33 and 39 C.	Not mentioned	Stomach; small and large bowel; rectum	Diffuse infiltration of stomach; localized infiltrations of bowel; many superficial ulcers	None	None	None	Acute anemia
18. Reinman, 1917	14; M	5 mo.	Hodgkin's disease (biopsy of cervical glands)	Severe abdominal pain; abdominal tenderness; dyspnea and dullness over sternum late	Not mentioned	White cells, 10,400; N, 71; M, 7; T, 9	Stomach	Four punched-out ulcers of cardiac end	Cervical; inguinal; mediastinal; periaortic	Spleen	None	Not specifically stated
19. Schlagenhauser, 1920 (case 3)	42; M	Large lymph gland, 1880; death, 1905	Lymphoma of the neck	No symptoms mentioned; abdominal distention; bleeding from nose and ears in 1905	Fever occasionally	Secondary anemia; white cells, 7,000	Colon	Small linear infiltrations with slight ulceration	Cervical; retroperitoneal	Spleen; liver	Anasarca	Not specifically stated

N. indicates neutrophilic polymorphonuclear leukocytes; L., lymphocytes; M., monocytes; T., transitionals, and E., eosinophils.

*Clinical and Anatomic Manifestations of Twenty-Six Recent Studies of Gastro-Intestinal Lymphogranulomatosis
Collected from the Medical Literature—Continued*

Case Number, Author and Date	Age and Sex	Duration and of Sym- ptoms	Clinical Diagnosis	Clinical Manifestations	Tem- pera- ture	Morphologic Blood Ex- amination	Part of Gastro-In- testinal Tract Involved	Types of Gross Change in the Gastro- intestinal Tract	Lymph Glands Involved	Other Organs Involved	Associated Pathologic Changes	Cause of Death
20. Hess, 1907	24; M	About 1 yr.	Cirrhosis of liver; secon- dary anemia; enlarged spleen	Moderate diarrhea; ab- dominal distention	Not men- tioned	Not men- tioned	Colon; rectum	Diffuse infiltra- tion	Cervical; lingual; mesenteric	Spleen	None	Not specifically stated
21. Sussig, 1924 (case 2)	42; M	6 wk.	Carcinoma of large bowel (Internist); tuberculous lymphoma of mesentery (surgeon)	Epigastric pain; an- orexia; nausea; marked diarrhea; loss of weight; distention of abdomen; fluid in abdomen; pal- pable mass in left upper quadrant; no lactic or free acid, total 6; no blood in stools	High fever, type not stated	Red cells, 2,420,000; white cells, 4,800; N., 78; L., 18; M., 3; E., 1	Jejunum; colon; rectum	Multiple small ulcers in jejunum, large bowel and rectum; perfora- tion of jejunal ulcer	Slight of ax- illary and lingual; mesenteric; retroperi- toneal	None	Ascites	Not specifically stated
22. Sussig, 1924 (case 1)	52; F	7 mo.	Ulcerative rectosig- moiditis	Onset with chills and diarrhea; rapid emacia- tion; no free acid, total acidity 9, and no lactic acid in stomach con- tents; enlarged follicles and large ulcers in sig- moid on proctoscopic examination	Periodic irregular fever reaching 40.2 C.	Red cells, 3,662,000; white cells, 3,200; N., 80; L., 5; T., 5; E., 0.5	Stomach; ileum; colon; rectum	Ulcer 2 cm. in diam- eter and multiple small ulcers in stomach; multiple pea-sized ulcers in ileum, colon and rectum	Mesenteric; retroperi- toneal	Spleen; liver	None	Not specifically stated; follow- ed marked hematemesis
23. Terplan, 1922	56; F	Several weeks	Intestinal tumors; ul- cerative en- teritis (tu- berculosis?)	Constipation early; diar- rhea; vomiting; an- orexia; firm palpable mass at left costal margin; no blood in stools	Intermit- tent be- tween 37 and 39 C. for one week; then normal	Not men- tioned	Stomach; small and large bowel	Many small ulcers and infiltrations in stomach; many ulcers in large and small in- testine	Cervical; mesenteric; perigastric; peripancr- eatic and peri- aortic	Spleen; liver	Ulcer of tongue; acute peri- tonitis	Peritonitis
24. Ziegler, 1911 (case 6)	52; M	1½ yr.	Not stated	Diarrhea at intervals; anorexia; severe eczema- toid skin lesion; disten- tion of abdomen; pal- pable liver	Intermit- tent be- tween 38 and 40 C.	Secondary anemia	Small bowel	Infiltration of lymph follicles	Cervical; ax- illary; praeclavicular; liver; auricular; axillary; tra- cheobronchial; mesenteric; retroperitoneal	Thyroid; lungs; kidneys; pleura; testicle	Peritonitis	Peritonitis
25. Weinberg, 1919	50; F	14 mo.	Pseudo- leukemia	No noteworthy symp- toms or signs except occasional diarrhea	Typical intermit- tent fever	Secondary anemia; normal white cells	Stomach; small bowel	Multiple small infil- trations in stom- ach; enlarged folli- cles and small ul- cers in intestine	Cervical; axillary; tracheobron- chial; mes- enteric	Spleen; liver; kidneys; trachea	Ascites; hydro- thorax	Not specifically stated
26. Drope, 1926	70; F	1 yr.	Myodegener- atio cordis; coronary arterioscle- rosis; athero- sclerosis; generalized hydrops	Weakness one year; en- largement of cervical lymph glands; diarrhea for three months; an- orexia	Remittent 38.2 to 37.8 C.	Not men- tioned	Stomach; small bowel	Multiple infiltra- tions of wall of stomach; small infiltrates of ileum and jejunum	Mesenteric	None	Arterio- sclerosis; hydrops; acute peritonitis; granulo-cell sarcoma of a rib	Acute peri- tonitis

N. indicates neutrophilic polymorphonuclear leukocytes; L., lymphocytes; M., monocytes; T., transitional, and E., eosinophils.

infiltrations of the surrounding organs by direct extension. The gastrointestinal infiltrations in the third were extensive and associated with an unusual and extensive distribution in the abdominal organs and abdominal lymph glands. The initial manifestations were subcutaneous infiltrations about the right cheek and upper right cervical region, which disappeared after roentgen-ray exposure, but which were followed by extensive lymphogranulomatous infiltrations of the stomach, rectum, sigmoid portion of the colon, ovaries, broad ligaments and retroperitoneal lymph glands.

REPORT OF CASES

CASE 1.—History.—D. B., a Greek laborer, aged 44, entered the Presbyterian Hospital, Chicago, May 27, 1924, on the service of Dr. B. W. Sippy presenting an illness which began thirteen months before with a cough and sore throat of one month's duration. This was followed by epigastric distress which lasted from twenty to forty minutes after meals. There was no nausea or vomiting. The epigastric distress did not radiate, and was not present during the night or before breakfast. Two months after the onset, severe diarrhea occurred and persisted six weeks. There were as many as from ten to fifteen stools per day and they contained much mucus but no visible blood. Following this, obstinate constipation was present. A constant dull boring pain was felt in the abdomen at the level of the umbilicus for from five to six months before admission to the hospital, and it was not relieved or accentuated by anything in particular. At first the pain was worse at night, but later it was equally severe during the day. Tarry stools or hematemesis were not observed. Loss of weight amounted to 30 pounds (13.6 Kg.) in the year before admission. Shortness of breath and marked pallor were present for two months. The past history was essentially negative except for occasional headaches during the last two years before examination and occasional sore throats.

Examination and Course of Illness.—Pallor and emaciation were marked. Carious teeth and pyorrhea were observed. The tonsils were enlarged and the vessels injected. The cervical lymph glands were not palpable.

The apex impulse was 9 cm. from the midsternal line. Cardiac murmurs or irregularities, or noteworthy alternations of the lungs, were not observed. The abdomen was well rounded, with a bulge in the upper umbilical and left hypochondriac regions due to a hard firm mass, which was markedly tender on deep palpation. The liver, spleen and kidneys were not palpable, and the rectal examination gave negative results.

The urine was normal. Occult blood was demonstrated in the stools by the benzidine test. The blood Wassermann reaction was negative. In an Ewald test-meal occult blood but no free acid was found, and the total acidity was 42. Lactic acid and Oppler-Boas bacilli were not present. Milk coagulation was complete at a dilution of 1 to 160. The hemoglobin content was 45 per cent and the red blood cells numbered 3,710,000 and the white blood cells 8,000. In the differential count there were 83 per cent neutrophilic polymorphonuclear leukocytes, 10 per cent small lymphocytes, 6 per cent mononuclears and 1 per cent basophils.

The fluoroscopic examination demonstrated that the stomach was much enlarged, the greater curvature being four fingerbreadths above the symphysis, and there was a constant, ragged, filling defect of the lesser curvature in the antrum. The duodenal cap was distinct.

Clinical diagnosis: Carcinoma of the stomach.

The abdominal pain became intense, required opiates for relief and was almost constant. The temperature was irregular, varying from 98 to 100 or 101 F. each day. Death occurred July 16, 1924.

Autopsy (C. W. A.).—"Anatomic diagnosis: Pseudoleukemia gastro-intestinalis; pseudoleukemic infiltrations of the liver, pancreas, gallbladder and parietal peritoneum (by continuity); spontaneous perforation of the stomach; acute generalized fibrinopurulent peritonitis; hyperplasia of the spleen and gastro-hepatic and peripancreatic lymph glands; moderate general anemia; marked emaciation; generalized icterus; cloudy swelling and fatty changes of the kidneys and liver."

The body weighed 120 pounds (54.4 Kg.), and was about 165 cm. long. The abdomen was distended. The skin and sclerae were pigmented yellow-green. Palpable superficial lymph glands were not found.

The lower margin of the left lobe of the liver and the lower margin of the right lobe to the right as far as the gallbladder were adherent to the upper surface of the stomach by fibrous adhesions. The lining of the duodenum was smooth and intact to the pylorus. The portal vein was grossly unchanged. The lining of the cystic, hepatic and common bile ducts was smooth and glistening. In the gastrohepatic ligament there were soft, moist, gray-red lymph glands, averaging 2 cm. in length. Similar light gray lymph glands were seen about the head of the pancreas. Those in the mesentery of the small bowel were only from 5 to 6 mm. in diameter. The outside of the stomach was generally light gray, mottled by a few green and brown places from 1 to 3 cm. in diameter where the surface was sunken. The front wall of the stomach was adherent to the parietal peritoneum in a place 15 by 9 cm., with the umbilicus in the center. The gallbladder at its tip was adherent to the stomach, its wall at this point being from 5 to 10 mm. thick from homogeneous gray tissue, but the lining was grossly unchanged. The wall of the stomach, except for a small part about 3 cm. wide at the cardiac end along the lesser curvature (which was normally thick) was from 1 to 4 cm. thick. Its inner surface was irregular from elevations from 1 to 10 cm. in diameter and from 1 to 2 cm. high. The gray tissue making up the wall of the stomach extended through the serosa and into the undersurface of the lower margin of the liver at the inner 10 cm. of the left lobe. The lining of the stomach, where the wall was infiltrated by the gray to gray-red adenoid-like tissue, was extensively ulcerated and discolored dark green to gray-green to gray-red. The margin of the mucous membrane at the ulcers was irregular and extended beyond the tissue beneath it. The front wall of the stomach was perforated in a place 3.5 cm. in diameter close to the greater curvature. The stomach (fig. 1) stretched out on a flat surface was 24 cm. from the pylorus to the cardia along the lesser curvature, and the maximum circumference was 35 cm. The greater curvature of the stomach was 50 cm.

The spleen weighed 395 Gm. and was soft, and the capsule was smooth and thin. Surfaces made by sections were light red-purple. The trabeculae were moderately prominent and the malpighian corpuscles sparse and the size of a pinpoint.

The lining of the rectum was light gray to light green, and normally thin. The lining of the urinary bladder was light gray and unchanged.

The outside of the kidneys was smooth, light gray-red to light gray-yellow. The cortical markings were slightly indistinct, and the cortices were from 8 to 9 mm. wide.

The lining of the pancreatic duct was smooth and intact. The body of the pancreas was almost entirely grown through by gray tissue like that in the wall of the stomach, but the tail and head were unchanged.

The wall of the small and large bowel was normally thin.

Free fluid was not found in the pleural cavities. The lungs were normally free. In the heart chambers and superior vena cava nothing but fluid blood was found. The tracheobronchial and mediastinal lymph glands were not enlarged.

Histology.—In several microscopic sections of the wall of the stomach, stained with hematoxylin and eosin, the changes were similar, except for the presence or absence of ulceration of the mucosa. The submucous, muscular and subserous

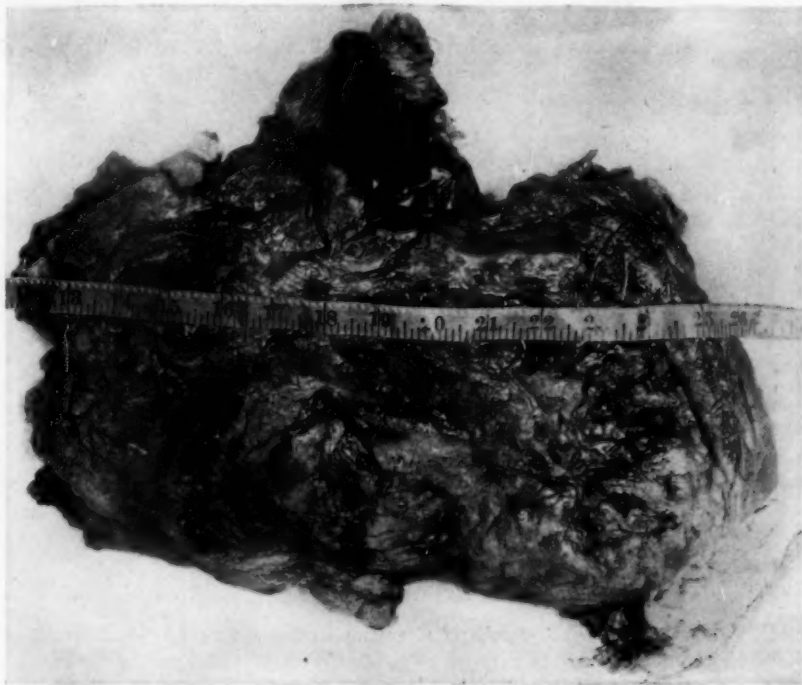


Fig. 1 (case 1).—The stomach, opened along the greater curvature and stretched out on a flat surface, is $13\frac{1}{2}$ inches (33.8 cm.) in circumference at the junction of the fundus and pyloric antrum; in the lining of the stomach there are extensive irregular ulcers with slightly elevated margins, and the wall is everywhere thickened except along the lesser curvature near the cardiac end; the pyloric end of the stomach is at the upper end of the photograph.

coats were densely infiltrated with irregular, discrete and interlacing regions, made up of several types of cells and a fine but abundant stroma. These regions altogether occupied slightly more than half of the sections, and the average number of cells in each region was about thirty. The regions were oval or slender, the long dimension usually parallel to that of the stomach wall. In the muscular coat, the infiltrations interlaced so as to separate the muscle cells into thin, interrupted bundles of from two to four cells. In the subserous layer the

infiltrated regions were separated by heavy bands of collagenous fibrous tissue. Where the mucosa was still present, only a few regions of infiltration were found in it near the muscularis mucosae.

The outstanding characteristics of the infiltrations (fig. 2) were the multiple types of cells and the irregularity of the cells in number and positional relationship. The predominating cells were lymphocytes and those characterized by a round, oval or irregular vesicular nucleus and abundant cytoplasm, the latter cells averaging 20 by 25 microns in diameter. There were also plasma cells, fibroblasts, occasional polymorphonuclear leukocytes, the eosinophilic variety scant, and multinucleated cells. The latter were predominantly represented by those with two nuclei, and those with four or more nuclei were sparse. The larger multinucleated cells resembled those originally described by Sternberg and Reed. Throughout there were "endothelial cells" undergoing mitosis, varying from typical mitotic figures to those formed of small chromatin masses arranged in

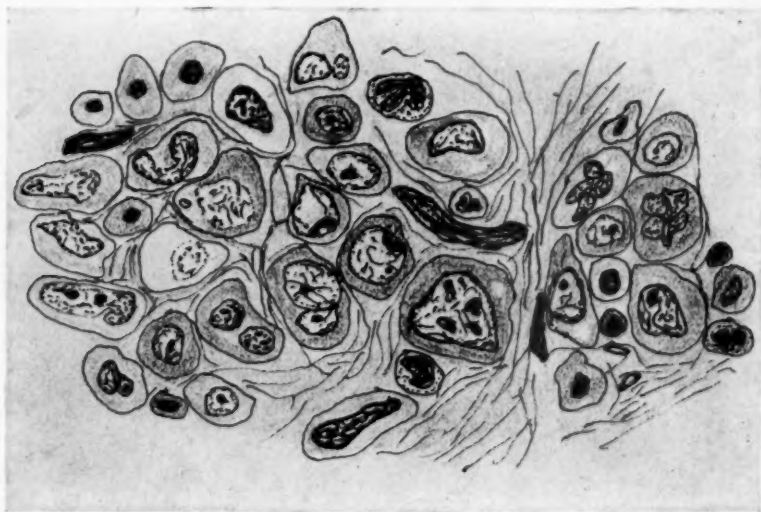


Fig. 2 (case 1).—The histologic alterations of the wall of the stomach are characterized by the multiplicity of cells, chiefly endothelial, multinucleated and round cells, and by a fine, interlacing, extensive stroma.

irregular squares or circles. Some of the nuclei were pyknotic. In some of the multinucleated cells, pale circular blue regions and pyknotic nuclei were found. Between the cells, abundant in some places, were small, round and irregular, solid, blue masses, most of them too irregular for bacteria, which probably represented chromatin masses from necrotic cells.

In a microscopic section of a peripancreatic lymph gland 1.5 by 1 cm., the normal architectural arrangement was obliterated by a more or less uniformly distributed granulation tissue, characterized by an abundant polycellular infiltration and a delicate stroma. The nuclei varied so in shape that there were hardly two of them alike. The predominant cell was one in which the nucleus was round or oval, with a moderate amount of chromatin, the nucleus from two to four times as large as that of a small lymphocyte, and the cytoplasm slightly greater in amount than the nucleus. Many had mitotic figures. The next most

abundant cells were small lymphocytes. Scattered throughout the section were large mononuclear cells, about one to every second or third high power field from 30 to 40 microns in diameter, with large vesicular nuclei, the cytoplasm faintly acidophilic. Multinucleated giant cells with from three to six nuclei were sparse. Along one margin, there were small lymph follicles and lymphatic cords, and the cells in the cords were chiefly small lymphocytes. Plasma cells and eosinophilic polymorphonuclear leukocytes were present.

In a microscopic section of a gastrohepatic lymph gland there were discrete and confluent, irregular, cellular regions, separated by loose acellular fibrous tissue of similar extent. At the periphery of the gland there were still small lymph follicles. The junction of the two regions was usually sharp.

In the body of the pancreas an extensive diffuse infiltration had widely separated the acini, but the cells of the latter were unchanged. The majority of the cells in the infiltration were epithelioid cells, lymphocytes and old and young fibrous tissue cells. Occasional plasma, giant and multinucleated cells were observed.

In several sections from the liver, there were round regions in the lobules, up to 0.1 mm. in diameter, and one or two to a section 1.5 by 1 cm., composed of polymorphonuclear leukocytes, young fibroblasts, lymphocytes and a few large cells with pale nuclei. Eosinophils were plentiful. In the periportal spaces in a few places there were slightly larger similar regions. Between the hepatic cords in many places a few polymorphonuclear leukocytes were found. The hepatic cords were intact and the central veins were small.

In one portion of the liver, the location unknown, about half of the microscopic section was made up of interlacing regions composed of erythrocytes. These regions extended from lobule to lobule and were not confined to the periphery or central portion. Many of the cells in the hepatic cords were necrotic.

The spleen in many microscopic sections was only slightly altered. Many of the malpighian corpuscles were small, and the central artery was frequently at the periphery. There was, on the average, one malpighian corpuscle to a low power field. The venous sinuses occupied at least one half of the sections. In the pulp many erythrocytes were present. Lymphocytes and polymorphonuclear leukocytes were the predominant nucleated cells in the pulp. The stroma was delicate. Throughout the splenic pulp, cells from 15 to 20 microns in diameter were seen, with round or oval vesicular nuclei. Occasional plasma cells were found.

No noteworthy change took place in microscopic sections of the myocardium, lungs, small and large bowel, prostate, aorta and kidneys.

In sections of the stomach, lymph glands and pancreas, stained with Giemsa's stain, as modified by Wolbach, an unsuccessful search was made for the intracellular mycelia-like bodies described by Kuczynski and Hauck in the multinucleated giant cells. In sections stained by the Ziehl-Neelsen method, acid-fast organisms were not found.

Histologic diagnosis: Lymphogranulomatosis of the stomach, pancreas, liver and perigastric, peripancreatic and gastrohepatic lymph glands; hemorrhage of the liver.

Summary.—Little in the clinical manifestations of this case yielded data usable in the differential diagnosis from carcinoma, except that without pyloric obstruction the cavity of the stomach was unusually large, and that the leukocyte count was only 8,000, and there was a decrease in lymphocytes.

The microscopic alterations in the wall of the stomach and regional lymph glands were typical of lymphogranulomatosis. The changes in regions in which

the mucosa was intact were slight in this coat, the extension of the infiltration being chiefly in the submucosa.

In all three of our cases the pancreas was infiltrated, and so similarly that sections from one case were almost identical with the others in distribution of the granulation tissue between the acini.

The disease began with an acute infection of the upper respiratory tract, but anatomic changes were not found in the cervical region.

CASE 2.—History.—Mrs. K. T., white, aged 38, was first seen by Dr. L. C. Gatewood in January, 1924, and gave a history of recurring chills and fever, and vomiting of fluid blood during two and one-half years. Epigastric distress was associated with difficulty in the passage of solid food through the lower end of the esophagus. Regurgitation did not occur. The patient suffered from pleurisy in 1922, and influenza in 1923. The remainder of the history was essentially negative.

Examination and Course of Illness.—Palpable cervical lymph glands were not found. A hard mass was present in the left hypochondrium, probably the spleen. The lung fields were clear in the roentgen-ray examination. Barium was arrested at the lower end of the esophagus, but there was a moderate sized passage through the cardiac orifice. The stomach was of the "J" type, the upper portion of the fundus being displaced by the spleen. Good peristaltic waves and a good duodenal cap were present. Colon fluoroscopy revealed a low splenic flexure, the upper margin flattened as if compressed from above.

During the next six months the stricture at the cardia was gradually dilated to admit from 32 to 35 French dilators. Dilation on June 4, 1924, was followed in two weeks by a chill, which recurred two days later. Nothing significant was observed in the chest or abdomen. On June 23, 1924, the patient was admitted to the Presbyterian Hospital, complaining only of chills and fever.

Palpable masses were not present in the abdomen, except the spleen which extended from two to three fingerbreadths below the costal margin. Tenderness and rigidity were not found.

The urine was normal. Occult blood was observed in the stools. The blood pressure was 86 systolic and 50 diastolic. The red blood cell count was 4,100,000, white blood cells 10,200 and hemoglobin content 70 per cent. The blood Wassermann reaction was negative. Blood was seen in the vomitus, but no free acid.

The lung fields were clear, as shown by the fluoroscopic examination. Barium passed into the esophagus with slight arrest at the cardiac orifice and just below the diaphragm extended outward toward the left into an irregular shadow approximately from 10 to 15 cm. in diameter, and then pushed down into a second shadow, apparently the stomach. An air bubble at the top of the lower shadow and raggedness of the upper shadow indicated that the two were entirely separate. A connection was not found between the colon and the pocket above the stomach in a simultaneous stomach and colon fluoroscopic examination.

Chills and fever continued after admission. A sharp sticking pain in the left upper quadrant and epigastrium, which radiated toward the back, occurred on June 26. Clinical diagnosis: Left subphrenic abscess.

On July 11, a gastrostomy was performed. After feedings were started through the gastrostomy opening, the subphrenic pocket gradually closed. When the patient began to eat by mouth, the perforation reopened. The stomach mucosa viewed through a cystoscope introduced through the gastrostomy opening was grossly unchanged. The patient left the hospital, September 25, taking food only through the gastrostomy and gaining in weight.

In February, 1925, epigastric pain occurred after each gastrostomy feeding, and by September the patient had lost 25 pounds (11.3 Kg.). She was readmitted to the hospital September 15, because of tenderness about the gastrostomy tube, pain after each feeding widespread over the lower part of the abdomen, fever, weakness and occasional nausea.

Dulness was present above and to the left of the gastrostomy opening, continuous above with the heart and liver dulness and extending as far as the right nipple line. The spleen was palpable on deep inspiration, and tenderness was found in the right upper quadrant in a palm-sized area below the costal margin.

The urine was normal. Occult blood was demonstrated in the stools. The red blood cell count was 4,600,000, the hemoglobin was 62 per cent, the white blood cell count was 7,700 and blood cultures were negative.

Barium passed directly into the stomach. The stomach was irregular in outline especially along the greater curvature in its midportion. There was a good duodenal cap and the second part of the duodenum filled. At the upper end of the stomach were two small linear shadows, one projecting toward the old subphrenic abscess, and the other toward the midline.

The patient continued to lose weight although the food intake exceeded 3,000 calories per day. The temperature was irregular, varying from 98 to 100 F. until October 23, when it rose to 103.4 F. and then continued with marked oscillations between 97.6 and 106 F. The patient died on November 2, following a gastric hemorrhage.

Autopsy (C. W. A.).—"Anatomic diagnosis: Chronic tuberculous ulcers (three) of the stomach; spontaneous perforation of a gastric ulcer into the spleen; abscess of the spleen; hyperplastic tuberculosis of the gastric, mediastinal and peripancreatic lymph glands; obliterative, left, subphrenic, fibrous peritonitis; healed gastrostomy; marked emaciation; thrombosis of the splenic vein; passive hyperemia of the spleen; free blood in the stomach and small bowel; marked general anemia; left apical, nodular caseous pulmonary tuberculosis; localized, left apical, fibrous pleuritis."

The body measured 152 cm. in length, and weighed only 90 pounds (40.8 Kg.). Body nourishment and muscular development were poor. The abdomen was scaphoid. The fossae of the thorax were all deep. Pigmentation and edema of the skin were not observed. A healed gastrostomy opening 9 by 5 mm. was seen 7 cm. above the umbilicus and 3 cm. to the right of the midline. On the skin about this opening fresh blood was found.

In the stomach, there was 300 cc. of dark purple, almost black blood. The front surface of the stomach was adherent to the diaphragm and lower ribs by firm fibrous adhesions. The spleen was pulled against the front wall by fibrous adhesions from the sixth to the ninth ribs, the upper pole in the nipple line. The spleen was also extensively adherent to the diaphragm. Gross changes had not taken place about the uterus and its appendages. The omentum was drawn upward and was adherent to the junction of the spleen and stomach. The lesser cavity of the omentum was obliterated by fibrous adhesions, most abundant between the pancreas and stomach. The splenic flexure of the colon was firmly bound to the greater curvature of the stomach.

A firm mass was present in the lower portion of the mediastinum immediately above the diaphragm, about 5 or 6 cm. in the largest dimension. The upper pole of the spleen pushed inward, compressing the upper portion of the fundus of the stomach and was tightly adherent to the left margin of the liver and front wall of the stomach.

The stomach, spleen, pancreas and left half of the transverse colon were intimately bound to one another by gray fibrous and gray soft tissue. In the front wall of the stomach 3 cm. from the greater curvature and 13 cm. from the pyloric ring there was a gastrostomy opening 2.5 cm. in diameter, with smooth margins. At the greater curvature 18 cm. from the pyloric ring and 20 cm. from the cardiac end, an ulcer 3 cm. in diameter was found with rounded margins, the wall of the stomach sloping up to the margins for from 2 to 3 cm. The ulcer was 1.5 cm. deep, the base being formed by the colon and pancreas, which were separated from the stomach around the ulcer by firm gray, lymphoid-like tissue and scar tissue from 5 to 15 mm. thick. The stomach was adherent to the medial surface of the spleen so that the two were inseparably bound together by thick gray tissue. In the center of this adherent region, 12 cm. from the cardiac end in the back wall of the stomach, close to the greater curvature, an ulcer was found 5 cm. in diameter, with rounded, elevated, jagged margins, that had perforated into the spleen in front of the hilum, the cavity in the spleen being 3 cm. deep and filled with soft gray-brown, necrotic, semifluid material mixed with blood. The greater curvature of the stomach cephalad to the spleen was tightly bound to the undersurface of the diaphragm. The left subphrenic space was almost obliterated by fibrous adhesions and gray, firm tissue. An ulcer 1.5 cm. in diameter was seen close to the cardiac end in the back wall, 2 cm. behind the greater curvature; it was depressed because of retraction of the scar tissue between the stomach, diaphragm and upper pole of the spleen. The ulcers, with the surrounding infiltrated regions, occupied about one half of the fundus, chiefly along the greater curvature. The remainder of the wall of the stomach was flexible. The lining of the duodenum was grossly unchanged.

The body and tail of the pancreas were tightly bound to the undersurface of the stomach by gray fibrous tissue from 1 to 2 cm. thick, which also occupied the space between the lower pole of the spleen, transverse colon and stomach. The margins of the pancreas at the tail were obliterated in a few places by the surrounding gray tissue.

Along the upper margin of the pancreas and lesser curvature of the stomach were found lymph glands from 1 to 2.5 cm. in diameter, and uniformly gray in surfaces made by sectioning.

Gross noteworthy changes were not observed in surfaces made by sectioning the head and body of the pancreas.

There were nodular consolidations of the apex of the left lung and extensive fibrous adhesions between the apex and the parietal pleura. Enlarged lymph glands were not present in the mediastinum. The mass at the lower end of the mediastinum was closely adherent to the esophagus and diaphragm, hard, nodular and about 5 cm. in length and 3 cm. in diameter, and surfaces made by sectioning were gray and shiny. The lining of the lower end of the esophagus was smooth.

Histology.—In microscopic sections of the fundus of the stomach stained with hematoxylin and eosin, where the mucous membrane was intact except for post-mortem digestion of the superficial portion, the wall was from 5 to 6 mm. thick. The muscularis mucosa was intact, and between a few of the glands, close to the submucosa, small infiltrations of lymphocytes, plasma cells and eosinophils had occurred. The subserous layer made up two thirds of the wall of the stomach. Throughout this layer there were chiefly fibroblasts and lymphocytes in an edematous fibrous tissue. In addition, large cells with abundant cytoplasm and vesicular nuclei, and a few plasma cells and eosinophils were seen. This granulation tissue was vascular near the muscular layer. Close to the peri-

toneum, the predominating cells were epithelioid cells and fibroblasts, and there were a few lymphocytes and plasma cells.

In a microscopic section of the adhesions between the fundus of the stomach and the liver, the infiltration was about 10 mm. thick, and about three fourths of it was made up of granulation tissue external to the muscular layer. Near the surface adjoining the liver, were found chiefly lymphocytes and epithelioid cells in a dense fibrous stroma. A few polymorphonuclear leukocytes were present in each low power field. Close to the liver there was one region about as large as a low power field, in which the central portion was made up of poorly stained fibroblasts and lymphocytes in a pink granular material, and three large multinucleated cells, the nuclei slender and about the size of small lymphocytes, and in one cell arranged in almost ring form. This cell contained between twenty and twenty-five nuclei; in the two other cells the nuclei were packed closely together and numbered about the same. The first cell contained an abundance of pink granular cytoplasm; in the other two, it was sparse. This region was surrounded by lymphocytes and fibroblasts in a dense stroma and resembled a tubercle.

Between the liver, spleen and stomach, in the regions of the fibrous adhesions and gray tissue, the granulation tissue was uniform throughout a section 2 cm. long and 1 cm. wide. The stroma was delicate and capillaries were numerous. Where the granulation tissue was attached to the liver, the junction was sharp, but there was not any capsule between the two, the granulation tissue entering between the hepatic cells for a distance equivalent to the width of several cells. The predominant cell was one characterized by a nucleus that was generally oval, but each one slightly irregular, two or three times as large as the nuclei of small lymphocytes, with abundant chromatin in vesicular arrangement and a variable amount of cytoplasm which averaged about the same in amount as the nucleus. These were scattered throughout the stroma in the same proportion, and made up two thirds of the cells. Lymphocytes were moderately abundant and polymorphonuclear leukocytes, present in all parts, were sparse. Throughout the section, giant cells from 30 to 50 microns in diameter were present, from one to two in each low power field, and the cytoplasm was slightly acidophilic. The nucleus of most of these cells was from 10 to 12 microns in diameter, relatively poor in chromatin and sometimes misshapen. In others, the single nucleus was smaller and the chromatin more compact, but not pyknotic. Still others had two nuclei. In sections prepared with Giemsa's stain, the chromatin of the larger nuclei of the giant cells was arranged as a fine network, and there was usually one large nucleolus. In most of the giant cells were found round vacuole-like regions from 1 to 10 microns in diameter. In a few of these, fragments of nuclei were seen. In the cytoplasm of some multinucleated giant cells erythrocytes were present. The threadlike bodies described by Kuczynski and Hauck were not found.

In a microscopic section stained with hematoxylin and eosin of a perigastric lymph gland 1 cm. in diameter little of the normal structure remained. At one end a few follicles were seen. In the surrounding cords lymphocytes predominated, but mononuclear giant cells and eosinophilic leukocytes were also present. In the remainder of the section, a cellular interlacing network, occupied more than one half of the section. Between the cellular regions, was a wide loose stroma with lymphatic channels. In the dilated channels there were chiefly free endothelial cells, but also many polymorphonuclear leukocytes, the eosinophils abundant. Large cells from 30 to 40 microns in diameter, with large oval, vesicular nuclei and an abundance of cytoplasm were seen throughout the interlacing cellular portions of the gland. One necrotic region as large as two

or three low power fields stained diffusely pink, but the framework was still visible. Multinucleated giant cells of the Sternberg type were present but sparse.

There was atrophy of the hepatic cords near the central veins and marked hemosiderin pigmentation of these portions. In the periportal spaces, occasional regions 0.5 mm. in diameter were composed of lymphocytes, a few epithelioid cells and fibroblasts.

In microscopic sections of the spleen stained with hematoxylin and eosin, the venous sinuses were markedly engorged and the malpighian corpuscles were sparse and small.

Histologic diagnosis: Lymphogranulomatosis of the stomach, pancreas, liver and peripancreatic, gastrohepatic, gastric and inferior mediastinal lymph glands; miliary tuberculosis of the wall of the stomach and fibrous adhesions between the stomach and liver.

Summary.—The clinical course differed from that of the reported cases of gastric lymphogranulomatosis in its duration and complications. The sequence of clinical manifestations, confirmed by the anatomic alterations, indicates that the disease started in the mediastinal lymph glands near the diaphragm or cardiac end of the stomach and produced partial obstruction of the lower end of the esophagus by compression. Later, the stomach perforated into the left subphrenic space, the abscess here healing slowly after feeding through a gastrostomy opening. After several months of improvement, an ulcer of the stomach perforated into the spleen, and cachexia and fever recurred.

The frequent relationship of lymphogranulomatosis and tuberculosis is again encountered in this case. Clinical evidence of tuberculosis was looked for repeatedly during life. The apical pulmonary tuberculosis anatomically was of recent duration, except for the apical fibrous pleuritis, and repeated fluoroscopic and roentgenogram examinations of the chest during life gave negative results. The gross anatomic diagnosis of tuberculosis of the stomach led to a search for tubercle bacilli in fresh smears of the wall of the stomach and lymph glands, and in microscopic sections of the wall of the stomach, and to inoculation of guinea-pigs with lymph glands. All examinations gave negative results.

The changes in the wall of the stomach were not characteristic, there being only scar tissue and scant granulation tissue. The few tubercles found in the wall of the stomach were misleading until the lymph glands and tissue between the stomach and pancreas were examined. This has been the sequence of interpretations of many of the localized forms, except that sarcoma or pseudoleukemia in some instances was diagnosed from the changes in the wall of the gastrointestinal tract.

CASE 3.—History.—Mrs. I. T., white, aged 44, was well previous to September, 1922, when, following three nose bleeds, she noticed a painless swelling the size of a cherry in the right submental region which rapidly increased until it had spread to the angle of the jaw. During April, 1923, tenderness developed at the right zygomatic process, persisted for one month, and was followed by a swelling below the zygomatic process, near the nose, and increasing discharge from the nose and slight lacrimation from the right eye. The masses were not painful at any time. Headaches were frequent.

She entered the Presbyterian Hospital, Chicago, May 8, 1923, on the service of Dr. E. H. Miller. The past history was essentially negative except that the right antrum had been drained four or five years before. She had two normal pregnancies, fourteen and eleven years previously, and one miscarriage eight years before.

Examination and Course of Illness.—The patient was obese. There was marked swelling of the right side of the face and neck, obstruction of the nose on the

left side, chronic moderate nasal discharge and slight tearing of the right eye. The tonsils were large, the right larger than the left. Two nodules about 1 cm. in diameter were seen at the lower margin of the right malar bone. A hard and fixed mass 4 cm. in diameter was palpated in the pterygoid fossa through the mouth. Nodular swellings were present along the lower margin of the mandible fixed to the bone, and a large fluctuant mass in the submaxillary space extended behind the ear. The chest, abdomen and extremities were normal.

The urine examination and the blood Wassermann test gave negative results. The white blood cell count was 8,300. Roentgenograms of the skull and chest were negative.

A piece of gland was removed from the right submaxillary region. In the microscopic sections made from the gland were found "uniform collections of various sized round cells with large nuclei and many contained mitotic figures" (a description will be given later under "Histology"). The patient was discharged from the hospital two days after entrance and was treated with roentgen rays.

She reentered the hospital July 30, 1923. The swellings of the face and neck had decreased in size, but an enlarged gland, the size of a walnut, had appeared at the lower third of the outer side of the right sternocleidomastoid muscle. The hemoglobin content at this time was 80 per cent, and the white blood cell count was 5,800. The gland was dissected from the subcutaneous tissue. The histologic diagnosis at this time was not definitely made, but it was thought that a malignant neoplasm of the sarcoma group was present (a description will be given later under "Histology").

The patient was readmitted to the hospital Jan. 2, 1924, because of bearing down pains in the abdomen which had been present for one month, constipation and abdominal distention of one month's duration and nausea of one week's duration. Pain in the abdomen was increased by bowel movement.

The abdomen was enlarged, dome-shaped, and a mass in the left umbilical region and the left lower quadrant extended to the midline in front, and was not freely movable and only slightly tender. The upper third of the vagina was hard and leathery, fixed anteriorly and posteriorly, the fornices were obliterated and the cervix was part of a large immovable mass resembling a "frozen pelvis." There was no vaginal discharge.

In the urine occasional hyaline casts and pus cells were found. The hemoglobin was 50 per cent, the red blood cell count 2,640,000 and the white blood cell count 7,000. The systolic blood pressure was 118, the diastolic 82. A differential blood count was not made at this time.

The abdomen increased in size, and the patient became dyspneic and unable to take food. Difficulty was experienced in giving rectal feeding because of an infiltration of the rectal wall. The temperature was intermittent in type, seldom exceeding 100 F. Death occurred on Feb. 5, 1924.

Autopsy (C. W. A.).—"Anatomic diagnosis: Pseudoleukemic infiltration of the omentum, rectum, ovaries, broad ligaments, stomach and duodenum; hyperplasia of the right cervical, periaortic abdominal, gastric, renal, biliary and iliac lymph glands; ascites; anasarca of the lower extremities; marked fatty changes of the liver; compression of the left ureter; left hydroureter and hydronephrosis; cholelithiasis; infarcted appendices epiploicae."

The body weighed 210 pounds (95.2 Kg.), and was 150 cm. long. Beneath a healed incision of the neck 6 cm. long, there was a movable nodular mass about 4 to 5 cm. in diameter.

Slightly turbid yellow fluid amounting to 5,500 Gm. was collected from the abdominal cavity. The subcutaneous fat of the midline of the trunk in front was lemon yellow and had a maximum thickness of about 3 cm. In the omentum, about 1 cm. below the lower margin of the transverse colon in the midline, a gray-red firm mass 4 by 1 cm. surrounded one of the veins. In front of the abdominal portion of the aorta gray-red firm masses were present beneath the peritoneum, beginning high up in the region of the renal veins and increasing in size toward the pelvis, so that at the brim of the pelvis a mass was formed behind the peritoneum, bound to the aorta, that could be spanned by two hands. The spleen and liver were normally free. Bands of fibrous adhesions were found between the gallbladder and the duodenum, the transverse colon and mesocolon. Large firm gray-red lymph glands along the lesser curvature of the stomach produced a mass from 4 to 5 cm. in diameter. A similar but smaller chain of lymph glands extended along the greater curvature to the first part of the duodenum. No enlarged lymph glands were found in the mesentery of the small bowel. A large mass, with a transverse diameter of 18 cm., 12 cm. from front to back, and the topmost part 7 cm. above the front of the lower end of the lumbar portion of the spine, extended up into the abdominal cavity from the pelvis. The appendix vermiformis was normally free.

The lungs were small and crepitant throughout. The heart was not any larger than the body's fist. Enlarged lymph glands were not seen anywhere along the thoracic portion of the aorta, in the mediastinum, along the trachea and bronchi or along the large vessels leading into the neck. No change had occurred in the lining of the inferior vena cava or common iliac veins.

Many large lymph glands were found about the renal vessels resembling those found elsewhere, all from 2 to 3 cm. long and forming a chain about 10 cm. wide. The kidneys were slightly larger than normal. The capsule of the right kidney stripped easily, leaving a smooth light yellow-gray surface. The cortex was 1 cm. wide, and the markings were slightly indistinct. The left kidney was smaller than the right. The calices of the left kidney were dilated, averaging 1 cm. in diameter. Both ureters were surrounded by large lymph glands. The wall of the left ureter was compressed where it passed through a firm mass of large lymph glands and fibrous tissue in the pelvis. Between the left suprarenal gland and the liver there was a firm gray-yellow mass about 10 cm. long and 1 cm. thick, resembling the enlarged lymph glands described elsewhere.

In the gastrohepatic ligament, there were several lymph glands 2 cm. long. In the portal vein and its tributaries, the common bile duct and the hepatic ducts, no gross change had taken place. In the gallbladder were found about twenty-five brown, faceted stones, all about the same size and shape, averaging from 5 to 6 mm. in diameter.

The lining of the urinary bladder was smooth, but the back wall was puffy. The rectum was surrounded by gray fibrous tissue intermixed with gray-red tissue like that in the lymph glands, altogether 3 or 4 cm. thick.

After the pelvic organs were removed en masse, some gray-red soft tissue was still adherent to the front of the sacrum and the sides of the pelvis.

The outside of the liver was mottled light gray and yellow, and the capsule was smooth. Surfaces made by sectioning the liver were uniformly light yellow. The liver weighed 2,300 Gm. The spleen weighed 170 Gm.

The lesser curvature of the stomach (fig. 3) was 16 cm. long, the greater curvature 40 cm. The inner surface of the front wall of the fundus was thrown into four or five folds, each about 1 cm. wide and from 1 to 2 cm. high, separated by furrows several millimeters wide, the folds linear but slightly curved. These extended from the cardiac end to the pyloric antrum. Along

the lesser curvature and at the back wall the surface of the stomach was flat, but multiple oval, round and irregular ulcers from 2 to 10 mm. in diameter and from 1 to 2 mm. deep were seen. About one fifth of the surface of the lesser curvature was so changed. In the lesser curvature, about 5 cm. from the pyloric ring, was an irregular S-shaped ulcer, the long dimension being 3 cm. and parallel with the lesser curvature. The maximum width was 10 mm., and the maximum depth from 7 to 8 mm. The cephalad half was deep and crater-like, the margins rounded and overhanging the ulcer. The caudad half opened out into the surrounding surface gradually, without sharp demarcation. In the fundus along the greater curvature close to the cardiac end a portion of the wall was flexible and only from 2 to 3 mm. thick. In surfaces made by sectioning the wall here, a thin layer of the gray tissue appeared beneath the mucosa. A section of this region 1 by 4 cm. apparently was not changed.



Fig. 3 (case 3).—The wall of the stomach is uniformly thickened, averaging about 1.5 cm.; the extensive infiltration in the submucous coat is shown in a surface through the wall at the upper end of the photograph, the mucous membrane at the undersurface; the ulceration of the mucosa is much less extensive than in case 1; the gyri-like inner surface of the stomach has been frequently described in this disease.

The outer surface of the stomach, especially along the lesser curvature, was irregular, because of nodular confluent masses beneath the serosa several millimeters in diameter. In surfaces made through the lesser curvature most of the wall was made up of light gray to grayish red homogeneous tissue bounded at the inner surface by a pale red layer about 1 mm. thick, except where there were superficial ulcers. At the outer boundary there was a layer of muscle about 1 mm. thick which was broken by gray streaks the same color as the tissue in the submucosa. Outside the muscle, in most places, there was a layer about 1 mm. thick, the same color as the tissue in the submucosa. The thickness of the wall of the stomach here varied from 1 to 2.5 cm.

The folds in the duodenum close to the pyloric ring were wider and less distinct than those 3 or 4 cm. from the pyloric ring where the lining was grossly unchanged.

In the descending portion of the duodenum from 15 to 16 cm. from the pyloric ring, a mass involved most of the circumference, the long dimension transverse was 5.5 cm., and it was 10 or 11 mm. high and 2.5 cm. wide. Close



Fig. 4 (case 3).—The infiltration of the wall of the rectum and sigmoid portion of the colon is characteristic of the diffuse types of infiltration of the gastro-intestinal tract in lymphogranulomatosis.

to this mass the wall of the duodenum was gray, opaque and slightly thicker than the uninvolved portion. Outside of the muscular layer this gray tissue was present in a layer up to 1 mm. thick.

The lining of the distal end of the rectum (fig. 4) for from 3 to 4 cm. was normally rugate. In the back wall 2 cm. above the anal margin there was a

single oval, smooth mass 13 by 8 mm. and 4 mm. high, the center being umbilicated and ulcerated in a place 1 mm. across. The inner surface of the rectum and sigmoid portion of the colon was everywhere made up of rounded and oval elevations with narrow and wide furrows between them several millimeters high and from 1 to 6 cm. long. The wall of the rectum internal to the muscular layer was from 2 to 8 mm. thick. The muscular layer was distinct in most places with occasional extensions from the submucosa through it. Outside the muscular layer there was firm grayish red tissue in the perirectal fat, in some regions only in streaks 1 mm. wide, in others in large nodular masses from 2 to 3 cm. wide. The infiltration in the perirectal tissue extended down to the anal margin where it was 1 cm. thick.

The lining of the vagina was smooth. The mass (fig. 5) in the region of the right ovary was 15 by 9 by 5 cm. In some places it was fluctuant, and



Fig. 5 (case 3).—The extensively infiltrated ovaries are brilliantly mottled with light brown and yellow regions, separated by shiny, translucent, pale gray, interlacing bands; close to necrotic regions are hemorrhages and engorged, dilated veins; the infiltration of the broad ligaments ends sharply at the lateral margins of the uterus.

here there were a few cysts from 1 to 4 cm. in diameter. The mass in the region of the left ovary was 9 by 8 by 5 cm., and in surfaces made by sectioning there were ten round, light gray-brown regions, sharply delimited, from 1 to 3.5 cm. in diameter, and separated by gray fibrous tissue. Some of them contained engorged blood vessels, and in one there was a gray-yellow region about 1 cm. in diameter resembling caseous material. The outside of the masses was lobular.

The uterus was 8 cm. long, 5 cm. wide and 2.5 cm. thick. The lining of the cavity was smooth. Beginning sharply at the borders of the uterus, the broad ligaments were 1.5 cm. thick, chiefly around the fallopian tubes and as

far as the ovarian masses. Surfaces made by sectioning the fallopian tubes were pink and from 3 to 4 mm. in diameter.

Histology.—In microscopic sections of the lymph gland removed at biopsy on May 8, 1923, stained with hematoxylin and eosin, a diffuse granulation tissue was present except in a part of one follicle. The stroma of the granulation tissue was sparse and divided the cells roughly into groups of from twenty to thirty, the groups, however, being confluent with others in many places. Lymphocytes and endothelial-like cells predominated, the latter adherent to the

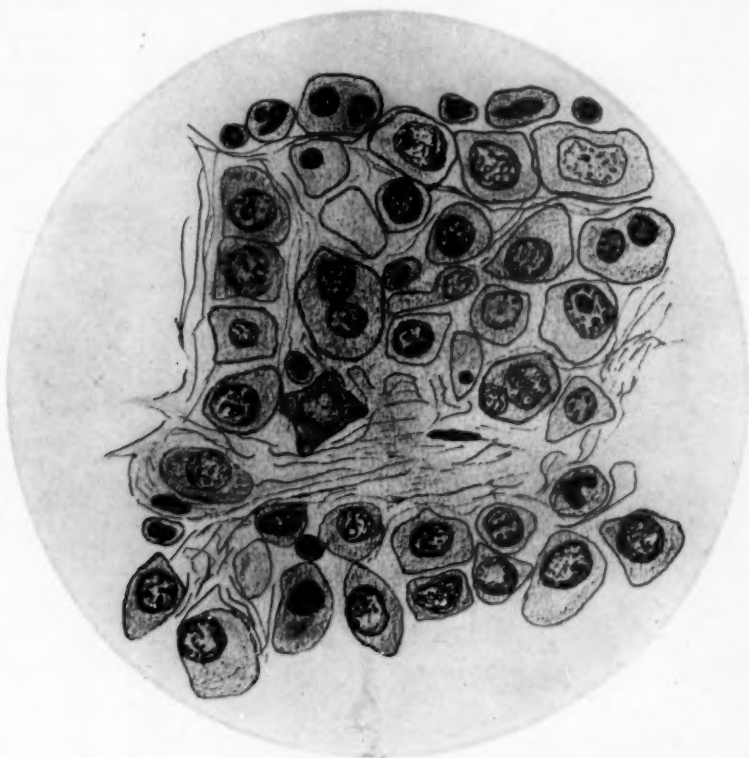


Fig. 6 (case 3).—The multiplicity of cells, the arrangement in groups from twenty to thirty and the predominance of large cells with vesicular nuclei, as indicated in the drawing of the wall of the stomach, are characteristic of the changes in other organs and lymph glands.

stroma and shaped to fit tightly one against another. Polymorphonuclear leukocytes were scattered sparsely throughout, and in every low power field eosinophilic leukocytes and plasma cells were seen.

In a microscopic section of the lymph gland removed on July 30, 1923, with a maximum diameter of 13 mm., the infiltration was diffuse through the lymph gland except for about ten or fifteen follicles most of which contained only a few cells, and practically no cells were observed in the germinal centers. The histologic changes in a low power field anywhere in the section were almost identical with a low power field picked at random elsewhere. In this lymph

gland, like the one removed in May, 1923, a slender stroma divided the cells of the infiltration into linear and oval confluent regions including from thirty to fifty cells. The predominant cell was of the endothelial variety. Lymphocytes were present everywhere and in some regions they were numerous. Eosinophils and plasma cells were plentiful throughout. The capsule in many places was invaded, lymphocytes predominating in these regions. Some of the lymph spaces under the capsule were filled almost completely with endothelial cells. The larger cells contained two, three and four nuclei, about ten or fifteen in the section.

In a section through the wall of the stomach where the mucosa was still intact and the wall was 1.5 cm. thick, between the muscularis mucosae and muscular layer a diffuse infiltration, quite uniform throughout, extended through the muscular coat in most instances down to the serosa. Throughout the infiltrated region a slender network of fibrous tissue separated the cells into groups of from twenty to forty cells, the interlacing network, slightly edematous, and in most of the bands of fibrous tissue only a few strands were present. The infiltration (fig. 6) here, as in the lymph glands removed during life, was characterized by diffuseness, predominance of endothelial cells and lymphocytes. With Mallory's eosin and methylene blue stain, even though the tissue was poorly fixed, eosinophilic leukocytes and plasma cells were numerous. The majority of multinucleated cells had only two or three nuclei and were numerous. The maximum infiltration was in the submucosa.

The alterations in the wall of the colon and duodenum were like those of the stomach. The same was true of the infiltrations in the pancreas and perirectal tissues and ovaries, except that in the latter there were huge regions of necrosis in which the structure of the infiltration could still be identified.

The histologic changes in the nodes from the perigastric and periaortic groups were almost identical with those removed before death.

In microscopic sections of the spleen, a single region 1 cm. in diameter was sharply circumscribed, but not encapsulated, with essentially the same histologic alterations present in the submucous coat of the stomach.

In sections of the liver obtained by freezing, stained with sudan III, fat was found in about 80 to 90 per cent of the hepatic cells. With hematoxylin and eosin, the nuclei of the hepatic cells were intact, but in the cytoplasm there were large vacuoles. Infiltrations like those in the wall of the stomach, were not present.

Histologic diagnosis: Lymphogranulomatosis of the stomach, duodenum, sigmoid portion of the colon, rectum, spleen, ovaries and broad ligaments, and of the gastrohepatic, perigastric, omental, periaortic abdominal, iliac and right cervical lymph glands.

Summary.—The correct diagnosis was not made in this case, although the only reliable diagnostic aid in lymphogranulomatosis was available, because the histologic alterations in the lymph nodes removed during life were misinterpreted.

The disease began in the right side of the face and some similarity to Mikulicz's disease was noted. In etiologic relationship, there was a history of right maxillary sinusitis.

Another unusual feature of the distribution of this disease was that the mediastinal and thoracic organs were uninvolved in the spread of the disease from the face to the abdomen. The distribution in the gastro-intestinal tract was also similar to that of the localized gastro-intestinal form, in that the stomach, duodenum and rectum were involved.

The extensiveness of the lymphogranulomatosis was somewhat inconsistent with the inclusion of this case as a representative of a localized form of the disease. It represented, however, an intermediate example between the purely localized and generalized forms. The alterations in the stomach grossly and microscopically were similar to those of case 1, which was a typical example of localized lymphogranulomatosis. In addition, gross alterations had not taken place in the spleen, even though the abdominal distribution was extensive.

The extensive fatty changes in the liver were not observed in other cases of gastro-intestinal lymphogranulomatosis. In this case they were probably related to anemia and acute inanition.

On the basis of the previous studies of this disease and the three cases herein reported, the following summary of the gross and microscopic alterations and clinical manifestations is presented.

GROSS MORBID ALTERATIONS

The lymphogranulomatous infiltrations of the gastro-intestinal tract are characterized by gray, translucent, adenoid-like tissue, and frequently by ulceration. The individual infiltrations vary from small elevations from 1 to several millimeters in diameter to diffuse infiltrations of long stretches of the gastro-intestinal tract. The infiltrations occur approximately in two types. The most common are multiple small infiltrations and ulcers of the stomach and bowel, typical examples of which are the cases of Eberstadt, Partsch, Terplan and Wallesch, and Kaznelson. Another characteristic type is represented by infiltrations that thicken the wall locally or extensively which is typically illustrated by the cases of Steindl, Pamperl and Terplan, and Hess, and by our first case. Usually, the infiltrations do not obstruct the lumen, but bowel obstruction from a local nodular mass was described by Catsaras and Georgontas, and de Groot, intussusception of the small bowel by Pamperl and Terplan and pyloric obstruction by Steindl. In most instances several parts of the gastro-intestinal tract are involved, the order of frequency being stomach, jejunum, ileum, colon and rectum. Unlike tuberculous ulcers, those in lymphogranulomatosis frequently involve the proximal portion of the gastro-intestinal tract.

The margins of the larger ulcers are usually elevated, surrounding the base like a wall, and sloping peripherally because of the infiltrated surrounding mucosa and submucosa. The base, according to most descriptions, is covered by a smeary, stringy material, stained by the gastro-intestinal content. A gross differentiating characteristic from tuberculosis, which is commonly confused with lymphogranulomatosis, is the absence of tubercles in the base of the ulcer and in the serosa.

The most common causes of death are cachexia, generalized peritonitis from perforation of ulcers and acute anemia from hemorrhage.

The distribution of the lymphogranulomatous infiltrations in other parts of the body, as previously mentioned, is variable, and although

the noteworthy gross changes in this group are in the gastro-intestinal tract and the clinical manifestations are largely dominated by these, in some the disease is disseminated. However, certain common differences from the generalized type are worthy of emphasis:

1. The liver and spleen are usually not enlarged, and nodular lymphogranulomatous infiltrations in them are uncommon.

2. The abdominal groups of lymph glands are most commonly infiltrated, and of these the mesenteric predominate. In a few instances, superficial enlargement has been reported, but it is unlike the common extensive enlargement so characteristic of lymphogranulomatosis or Hodgkin's disease in its generalized form.

HISTOLOGY

In a majority of the studies of this localized form of lymphogranulomatosis, the histologic report consists of a declaration that the changes are typically those of lymphogranulomatosis and that the so-called Sternberg or Reed giant cells are present. However, when the histologic changes are described one finds the same variations from the classic or formal accounts of Hodgkin's disease as are reported for this disease in other parts of the body. Occasionally, the changes in the gastro-intestinal tract can be classed only in the general group of granuloma or, in others, as hyperplasia of lymphoid tissue, the diagnosis being made from more characteristic changes in the lymph glands. On the other hand, in the lymph glands there may be only hyperplasia, and the typical changes are in the wall of the bowel and stomach.

The infiltrations are most common in the mucosa and submucosa. In the small regions the glandular portions are elevated and separated by the underlying infiltrations. Ulceration, however, rapidly occurs, presumably from local anemia of the mucous membrane. The muscular coat offers little resistance to the infiltration, bundles of muscle cells being separated into thin layers. Invasion of the subserous tissues is less common, but soon occurs in the extensive infiltrations. Small regions of necrosis are common.

The predominating cells are usually lymphocytes and "endothelial" cells. Sternberg-Reed cells have been sparse in most instances. Plasma cells and eosinophils vary in number. The stroma of the infiltration usually separates the infiltrating cells into irregular clusters, producing the characteristic microscopic architectural change of lymphogranulomatosis.

CLINICAL SYMPTOMS

The variety of clinical diagnoses listed in the table represents accurately the variability of the clinical manifestations. The obstacles to correct clinical diagnosis are apparent, if the following factors are considered: the infrequency of the disease; the lack of specific diag-

nostic tests for lymphogranulomatosis except histologic examination; the multiplicity of gastro-intestinal alterations, and the lack of enlargement of superficial lymph glands and the spleen so characteristic of the common clinical conception of lymphogranulomatosis.

In spite of the multiple clinical diagnoses so far made in this group, one is impressed, on reading the clinical descriptions, with a certain similarity in the history and clinical manifestations of a large group of these cases. Outstanding among the common features are diarrhea, abdominal pain, rapid cachexia, secondary anemia, leukopenia or normal leukocyte count and fever. Diarrhea was profuse and watery, but occult blood was uncommon. Abdominal pain was frequent and directed the attention of the clinician to the gastro-intestinal tract. The relation of pain to other abdominal manifestations was not clearly enough studied to allow a definite characterization of this symptom. Rapid cachexia and secondary anemia were usually so pronounced that a diagnosis of carcinoma or tuberculosis was made. A normal or low leukocyte count in the presence of fever is another feature of those cases in which a blood examination was made. The most common variations in the differential count were an actual decrease of lymphocytes and a slight eosinophilia. The majority of cases occurred in the fifth and sixth decades of life.

In regard to differential diagnosis, the cases approximately fall into three clinical groups that resemble other more common clinical entities. In order of frequency, these are: ulcerative enteritis and colitis, particularly tuberculous; gastric carcinoma; and bowel obstruction.

SUMMARY

Lymphogranulomatosis localized chiefly to the gastro-intestinal tract is being reported with increasing frequency. This disease has not been recognized at necropsy or by clinical examination, except when opportunity arose to examine tissue microscopically.

Many of these cases so far described have been confused anatomically with lymphosarcoma, tuberculosis, carcinoma and pseudoleukemia.

Twenty-six instances are reviewed, and three new cases are described.

The gross and microscopic anatomic alterations and the clinical manifestations are summarized.

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Laboratory Methods and Technical Notes

A MODIFIED TYPE OF AUTOPSY TABLE*

SCHIELDS WARREN, M.D., BOSTON

In the new Palmer Memorial Hospital, a special effort is made to secure as many autopsies as possible. This hospital is primarily devoted to the care of patients having cancer, and in this disease perhaps more than in any other, the autopsy is of great importance not only from the point of view of checking the results of treatment but from that of study-



Fig. 1.—Appearance of autopsy table.

ing the behavior of the disease. To this end the mortuary of the hospital has been carefully fitted with efficient apparatus, with due regard to attractive appearance. The autopsy room is one of the show rooms of the institution, and every effort is made to keep it dignified and neat.

In considering the type of table to be used, it at once became obvious that the usual stock tables supplied by surgical houses were not suitable. An extensive study of tables in different hospitals, particularly those in

*From the Pathological Laboratory, Palmer Memorial Hospital, and the Department of Pathology, Harvard University Medical School.

the neighborhood of Boston, was made, and a modification was attempted which would unite the valuable features of the various tables and eliminate, so far as possible, the bad points.

It was decided to construct the table of durable material, with an attractive white porcelain finish in order to fit it into the general scheme of the room. Figure 1 shows a corner of the room and the table. The table measures 30 by 84 inches, and the top of the grating is 36 inches from the floor. The sides are carried down in funnel fashion, forming the central drain, the opening of which is 6 inches square. The top of the table consists of three pieces of removable brass grid work, $\frac{1}{4}$ inch rods with $2\frac{1}{2}$ inch mesh. The outer edge of the

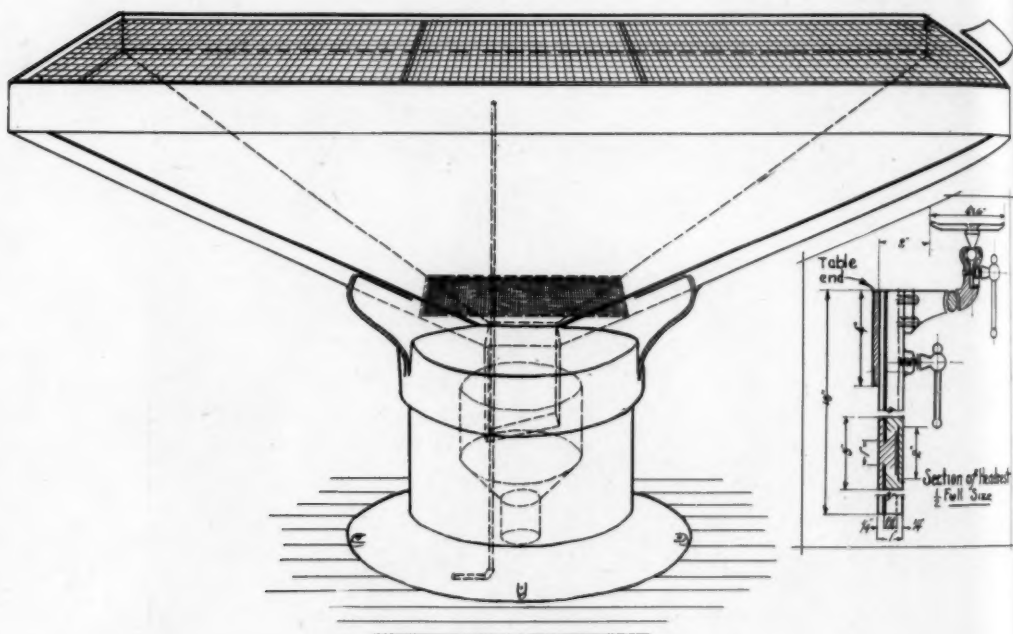


Fig. 2.—Diagram of autopsy table.

table is continued 1 inch higher than the grid, to prevent fluids from slopping over onto the floor. With this amount of space, it is possible to roll a body completely over, and, as the grid work is carried the full length of the table, to wash the body without inconvenience or splashing. A considerable experience working on the grid-topped table of the Boston City Hospital emphasized the value of the grid in preventing fluids from slopping on the floor.

The upper portion of the table sets on a hollow pedestal 18 inches in diameter, about which it revolves on a bronze ring. Inside the hollow pedestal is a sleeve, 12 inches in diameter, surrounding the drain from the upper portion of the table and leading down to a 3-inch connection with the sewer. Through this sleeve a single pipe projects which is connected with both the hot and the cold water system, with control cocks located on the wall. Surrounding both water pipe and sewer and continuous with the air space in the hollow pedestal is a ventilation duct which leads to a fan and a separate air duct to the roof. This fan is

controlled from the autopsy room and serves to give a downward draft through the table, thus preventing odors from becoming disseminated through the room. The advantage of this can readily be appreciated by any who have performed postmortem examinations on patients who have died from an advanced form of cancer.

Attached to one end of the table is an adjustable head rest which can be dropped considerably below the level of the table or raised several inches above it, and which serves to take the place of the customary block of wood which is placed beneath the neck. For this suggestion, I am indebted to Professor S. B. Wolbach. The head rest is not perfected as yet, but I believe it is possible to make it an adjustable head-holder rather than merely a head rest, and various types of holders are being tried.

Figure 2 will serve to clarify the description of the table, which was made by the Kny-Scheerer Corporation from my specifications.

A MODIFIED METHYLENE AZURE B STAIN FOR SECTIONS OF HUMAN HEMATOPOIETIC ORGANS*

MAURICE N. RICHTER, M.D.

NEW YORK

Until recently, methylene azure B (trimethyl-thionin) was considered unsuited for use in staining sections of tissue. MacNeal and Otani,¹ however, found it to be of special value for staining neutrophilic granules in sections of human tissues. For this purpose it is excellent. However, although precise in its staining of nuclei and granules, azure B is insufficient for the demonstration of basophilic cytoplasm in some cells (lymphocytes, plasma cells and immature cells of various types).

The best method previously described for staining human neutrophilic granules in sections is that of Ellermann,² which, however, is essentially a technic requiring methylene blue and which lacks the qualities obtainable with methylene azure. Ellermann's preliminary treatment increases the consistency with which good results may be obtained.

Although individual requirements play an important part in judging staining results, the newness of the azure B method prompts the description of a modification which has, for my purposes, given somewhat more satisfactory results.

* From the First Medical Division (Columbia University) and the Pathological Laboratories, Bellevue Hospital.

1. MacNeal and Otani: *Am. J. Path.* **2**:478, 1926.

2. Ellermann: *Ztschr. f. wiss. Mikr.* **36**:56, 1919.

MODIFIED TECHNIC

1. Fix (*A*) pieces not more than 2 mm. thick, by Ellermann's^a method:
 Twenty-four hours in *freshly* prepared mixture of Zenker
 (without acetic acid)..... 9 parts
 Neutral formalin (40 per cent formaldehyde)..... 1 part
2. Wash in running water, from twelve to twenty-four hours.
3. Embed in celloidin (*B*) (or paraffin).
4. Attach sections to slide by albumin and remove celloidin with absolute alcohol and ether (*B*) (or paraffin with xylene).
5. Absolute alcohol, one minute.
6. Ninety-five per cent alcohol containing tincture of iodine, fifteen minutes.
7. Eighty per cent alcohol until iodine is removed.
8. Water: several changes to remove alcohol.
9. Stain fifteen minutes, while steaming (*C*) in freshly prepared mixture of
 Erythrosin, 1 per cent aqueous..... 5.0 cc.
 Neutral formalin 0.25 cc.
 Eosin or phloxine may be substituted for erythrosin.
10. Rinse in distilled water.
11. Stain from one to five minutes in:
 Methylene azure B bromide 0.1
 Methylene blue U. S. P. medicinal..... 0.1
 Distilled water, or preferably buffer solution, p_H 7.5... 100.0
 The buffer is made by adding 15 cc. of a fifteenth molecular solution of primary potassium phosphate (9.078 Gm. to 1 liter of distilled water) to 85 cc. of secondary sodium phosphate solution (11.876 Gm. to 1 liter).
12. Flood from dropping bottle with several changes of absolute ethyl alcohol, until stain ceases to come out (ten seconds at least). Avoid water and lower alcohols.
13. Differentiate in:
 Clove oil 3 parts
 Absolute ethyl alcohol 1 part
 Colophonium, sat. alc. solution..... a few drops
 Control the differentiation under the microscope.
14. Place for thirty seconds in (*D*):
 Xylene 9 parts
 Amyl alcohol 1 part
 The differentiating fluid must be thoroughly removed.
15. Pure amyl alcohol, until ready to mount.
16. Mount in euparal, preferably the green variety.

RESULTS

The nuclei are a deep blue-black and the chromatin is sharply stained.

The nucleoli are distinct. The cytoplasm is various shades of lavender, red or blue, depending on cell types. The eosinophil granules are red, the eutrophil granules slightly darker red, and the basophil granules blue. The centrosomes are a bright red. The spindle fibers are usually red, and sometimes are purple. The fibrin is red or purple, depending on the degree of decolorization. The bacteria are blue.

NOTES ON THE METHOD

A. The fixation is of fully as great importance as the stain, especially for the staining of neutrophilic granules and centrosomes. If properly fixed, neutrophilic granules may be demonstrated, though perhaps not as clearly, by several other methods. Fresh tissues give the best results, but granules can usually be stained in specimens fixed up to twenty-four hours after death.

B. My preference is celloidin. Sections are cut at 6 or 7 microns. The method of fastening them to the slide and removing the celloidin has been described by Maximow and Danchakoff and more recently by Addison.³ Removal of the celloidin is essential; otherwise, it will be stained and obscure the picture.

C. Formalin added to the erythrosin intensifies the staining of the granules, though it is not essential. If it is omitted, the time of staining should be prolonged. Steaming the solution also intensifies the stain. Complete evaporation should be avoided.

D. After differentiation of the stain, several courses are open: The slide may be passed through xylene and mounted in neutral balsam, dammar, or cedar oil; it may be washed thoroughly in absolute ethyl alcohol and mounted directly in euparal, or amyl alcohol may be substituted for ethyl alcohol.

Euparal is a mountant that deserves more popularity than it has at present.⁴ Foremost of its advantages for the technic under consideration is its preservation of methylene azure and similar stains. Sections and blood smears mounted in euparal up to five years ago (azure II-eosin, Dominici's stain, Ellermann's, Wright's, Giemsa's and similar methods) have not faded, whereas some of the controls in supposedly neutral balsam are now worthless.

Euparal will clear and mount directly from 95 per cent alcohol if desired, but thorough dehydration is necessary to prevent fading of azure stains. Some preparations of euparal will mount from xylene, but other samples become cloudy. If this occurs, the "essence" of euparal should precede the euparal.

Amyl alcohol is also a valuable agent,⁵ as it is miscible with ethyl and methyl alcohols (95 per cent or absolute), xylene, and euparal or its "essence;" it evaporates slowly; it does not extract azure, eosin or hematoxylin stains and does not extract moisture from the air. In step 14, described in the foregoing technic, it prevents clouding of the xylene by traces of water.

MacNeal and Otani recommended their method particularly for the demonstration of neutrophilic granules. I am unable to find much difference in this respect from the results obtained by Ellermann's technic. However, by the modifications described, I have obtained good staining not only of the neutrophilic granules but also of centrosomes in some cells (lymphocytes, plasma cells, myelocytes, fibroblasts, giant cells and some tumor cells), with differentiation of the chromatic and achromatic elements of the mitotic spindle. Fibrin and bacteria are also clearly stained. The staining of centrosomes is of interest because they have not previously been reported in blood cells by a technic employing azure-eosin. The stain cannot, however, supplant standard cytologic methods for these structures.

The method described is applicable to general pathologic histology, particularly for the study of human hematopoietic organs.

3. Addison, in Piersol's Normal Histology, ed. 6, 1927, p. 443.

4. Lee: Microtometist's Vade-Mecum, ed. 8, 1921, p. 227.

5. Hollande: Compt. rend. Soc. de biol. **81**:223, 1918.

General Review

HETEROPHILE ANTIGENS AND ANTIBODIES *

I. DAVIDSOHN, M.D.

PHILADELPHIA

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* From the Research Institute of Cutaneous Medicine and the Pathological Laboratories of the Mount Sinai Hospital.

The concept of a strict specificity of the antigen-antibody relation had to undergo various modifications even in the early days of immunology. The most striking revision, however, became necessary after the discovery of heterophile antigens and antibodies.

DEFINITION

The term heterogenetic antibodies applies to antibodies that react with an antigen entirely different from and phylogenetically not related to the one instrumental in their production. Heterogenetic antigens are those antigenic substances which are able to stimulate the production of heterogenetic antibodies. The term heterogenetic is not a good one, especially when applied to antibodies, as it is the combining power of the latter and not their genesis in which one is interested. In 1917, Friedemann suggested another term for those antibodies, calling them heterophile, which I think is more appropriate than the other terms used. In this paper I shall use the term heterophile instead of heterogenetic.

FORSSMAN'S FORERUNNERS

Although it was Forssman in 1911 who, by his discoveries, gave an impulse to the prolonged and still continuing discussion on heterophile antigens and antibodies, I could find in the literature some attempts in this direction before Forssman. By injecting rabbits with sheep spermatozoa, Moxter, in 1900, produced an immune serum which was spermatozoocidal and also lytic for sheep corpuscles. An antibody was produced which acted on an antigen; although this antigen came from the same animal, it was not identical with the one used for its production. The fact that the antibody had a stronger affinity for spermatozoa than for sheep cells is not in accord with the characteristics of a heterophile antibody, as will be seen later in the discussion. It is also possible that the spermatozoa injected into the animals contained an admixture of red blood cells, no matter how minute it might have been. Michaelis and Fleischmann, in 1906, injected the livers of mice and guinea-pigs into rabbits and obtained antibodies not only for those organs, but also for the red blood cells of the respective animals. I am inclined to believe that the organ emulsion contained red blood cells despite the careful washing.

In 1907, Frouin immunized rabbits with an acetone extract of the yolk of chicken's eggs and obtained a lysin for the red blood cells of the dog. In 1911, together with Lisbonne, he reported further experiments which showed that the lysin so produced also laked the blood of the horse, goat, lamb, chicken and ox. The results were not uniform. The lysin was inactivated by heating at 56 C. for one-half hour and was reactivated by the addition of complement. It lost the hemolytic quality when dialyzed through a semipermeable membrane. That

observation was announced in the same year in which Forssman published his discoveries. It seems that the results of Frouin and Lisbonne justify giving them the credit for the production of the first heterophile hemolysin. It is due only to the short and rather incomplete report that their publication did not attract as much attention as it deserved

FORSSMAN'S PUBLICATION (1911)

In 1911, Forssman injected rabbits with the kidneys, suprarenals, liver, testicle and brain of guinea-pigs and obtained a lysin for the blood cells of sheep. A lysin could not be obtained when the blood cells of guinea-pigs were used for immunization. It was found to be specific, and did not act with the blood of the ox or the hog and what is still more important, it did not act with the blood of the animal whose organs were used, namely, the guinea-pig. Kidneys and suprarenals proved to give the highest titers. The organs were crushed in a dish, suspended in an 0.8 per cent solution of sodium chloride, filtered through linen and injected intraperitoneally or intravenously. Some guinea-pigs were bled, others were washed with an 0.8 per cent solution of sodium chloride until free from blood, without apparent influence on the result. Except in the former case, the lysin behaved differently toward the blood cells of guinea-pigs as had to be expected. With intraperitoneal injections high titers were obtained of from 2,000 to 3,000 units, and with intravenous injections of 8,000 units (a unit being the quantity of lysin necessary to lysis 0.1 cc. of 5 per cent washed sheep cells, adding 0.1 cc. of guinea-pig serum, provided this amount did not produce hemolysis by itself). The mixtures were incubated at 37 C. for one hour. Different quantities of organ emulsions were tried out, and it was found that as little as 0.3 Gm. of the kidney (it was naturally much less in the filtrate) was sufficient to cause production of lysin when injected into the peritoneal cavity and still less, 0.1 Gm., when administered intravenously. As large quantities as 8 Gm. of liver were distinctly less effective than smaller quantities. The value of these results was enhanced by the fact that Forssman titrated the sheep lysin present normally in rabbit's blood, the highest normal titer being 0.05 cc. More recent workers have found higher values for the natural anti-sheep lysin in rabbits, the highest being 0.02 cc. When the lysin so produced was mixed with a suspension of the organs of the guinea-pig, it lost the lytic quality. The organs of the cat and horse behaved similarly to those of the guinea-pig. These animals form the so-called guinea-pig group. The organs of the rabbit, ox and rat, and yeast and typhoid bacilli were unable to stimulate the production of sheep lysin when injected into rabbits or to absorb heterophile antibody; they belong to the so-called rabbit group.

There was one contradiction in Forssman's experiments: his heterophile hemolysin was not absorbed by a suspension of the liver of guinea-

pigs. He used this as an argument against Ehrlich's conception that the substance which causes the production of antibodies is identical with the one which combines with the antibody. This contradiction was due to faulty technic, as shown later by other workers. Forssman's hemolysin had some features in common with the usual antisheep lysin produced by the injection of the blood of sheep. Heating to 56 C. for one-half hour is well resisted by both, and both are reactivated by guinea-pig complement but not so completely by the complement of the rabbit; both are promptly fixed by sheep cells at 0 C. and 37 C. Sheep cells combine with much larger quantities of the heterophile lysin than of the other. The antisheep lysin present normally in the rabbits behaved just like the heterophile. Although guinea-pigs contain a natural antisheep lysin, the injection of organs of guinea-pigs did not increase its titer.

This was a thorough presentation of the problem. Almost every phase of it was touched, and it is therefore natural that it received a great deal of attention. Most of the work done later is a direct continuation of the work started by Forssman. Some new phases, however, have been developed.

Toxicity for Guinea-Pigs.—The rabbit serum has a marked toxicity for guinea-pigs, which is increased when the rabbit is treated with an antigen. Friedberger and his school have done valuable work in connection with this problem. According to his theory, the toxicity is due to the simultaneous presence of antibodies and an antigen remnant, which are together in the blood of the original host; when injected into a guinea-pig, however, they act by producing an anaphylatoxin. Doerr and Moldovan found that the toxic substance of the antisheep lysin could be removed from it by a single absorption with sheep cells, or by repeated absorptions with heterologous (guinea-pig, horse) red blood cells. The toxic effect does not disappear but is then carried by the cells. The toxic process is due to anaphylaxis. Subcutaneous injections of antisheep lytic serum caused a necrosis of the skin in guinea-pigs.

Various attempts were made to explain the toxicity of the normal and immune rabbit serum for guinea-pigs. Friedberger's theory of the antigen remainder was attacked and could not withstand criticism. It was found by von Dungern that the toxicity remains long (sixty days after injection) when there is hardly any antigen left. Doerr and Weinfurter could not find any antigen in rabbit serum on the tenth day, while the toxicity was then at its peak. In most experiments with horse and sheep protein the antigen disappeared before the fourth day, while the toxicity continued until the twentieth day. The highest toxicity of a rabbit serum obtained by immunizing with sheep cells was 0.03 cc. per hundred grams of guinea-pig. Doerr and Weinfurter thought that

the action of the heterophile organs which were used to produce in the rabbit a serum toxic for guinea-pigs is not specific. They found also that after the rabbits were bled there was an increase in the toxicity of the serum for guinea-pigs to about three times the original. It was not due to destruction of body proteins, as shown when rabbits were starved, since their serum did not increase in toxicity for guinea-pigs.

In 1912, Forssman and Hintze undertook to explain the primary toxicity of the heterophile immune serum for guinea-pigs on the basis of the former's discovery. Both the sheep cells and the organs of the guinea-pig contain antigen which causes the production of antishoop lysin. Both antibodies combine with the same receptors of the sheep cells. It may be assumed that the organs of guinea-pigs contain a sheep anaphylactogen, and probably also the substance which combines with the anaphylactic reacting body. It is possible that this substance combines also with the anaphylactic reacting body produced by the injection of sheep cells, and thus causes an anaphylactic reaction; as that substance is present in the organs of guinea-pigs, the combination of the two would occur in the organs. Experiments showed that the toxic substance in rabbit serum was absorbed by sheep cells and the kidneys of guinea-pigs and cats, while serum treated with emulsions of non-heterophile organs retained its toxicity.

A heterophile sheep lytic serum was injected intraperitoneally into a guinea-pig, and twenty-four hours later another heterophile serum was injected intravenously into the same animal. The guinea-pig survived. An isophile lytic serum produced by injections of the blood of sheep in the rabbit was injected into a guinea-pig intraperitoneally, and in twenty-four hours a heterophile serum was given intravenously; the animal died. This shows that only serums of a similar character produce antianaphylaxis, and that the toxic substances in the two are different.

The earliest publications stated that there was no apparent quantitative relation between the toxicity and the amount of antibodies present in the blood serum of the rabbit. Friedberger and Goretti obtained heterophile immune serums of a high lytic titer but not toxic for guinea-pigs. The height of the toxicity did not correspond with the height of antibody development. While the antibody showed a decrease, the toxicity was increasing. The amboceptors of isophile and heterophile immune serum were destroyed by lower temperatures than the toxic principle. In 1927, Hyde also found that the toxicity of ox serum for guinea-pigs was not influenced by heating at 60 C. for thirty minutes.

Doerr and Pick showed that the heterophile antibodies were fixed by organ cells of the guinea-pig. Two cubic centimeters of a highly lytic heterophile serum (complete hemolysis with 0.0008 cc. and a fatal dose of 0.4 cc. for 200 Gm. of guinea-pig) were injected into a guinea-pig. It was killed five minutes later, and the serum did not give any

lysis even in a dose of 0.3 cc. The same experiment was repeated with a rabbit the serum of which did not act in a dose of 0.3 cc. before injection and afterward laked in a dose of 0.01 cc. The same behavior was observed in rats. The experiment shows that the antibody combines in the guinea-pig with the antigen and disappears immediately, while it remains in the rabbit and rat and only becomes diluted. Similar results were obtained by Friedberger and Goretti.

It was expected that all of the animals belonging to the guinea-pig group would be susceptible to the toxic substance in the heterophile immune serum. Pick and Doerr showed that such is the case in dogs and chickens, while animals of the rabbit group are not affected.

The death of the guinea-pigs injected with heterophile serum was not due to the changed coagulability of the blood, although almost all autopsies showed thrombosis on the right side of the heart. Guinea-pigs that received hirudin prophylactically died, although their blood did not coagulate. Forssman thought that the death of the guinea-pigs was due to the action of the antibodies on the brain. This was definitely disproved by later workers. Pick and Doerr had already suspected a primary lesion in the endothelium of the blood vessels. This was definitely shown by Halber, in 1924, when she found heterophile antigen in the endothelial cells of the aorta of animals belonging to the guinea-pig type. She was able to produce powerful heterophile immune serums by using this antigen. Since Forssman's work, it had been found that by injecting a heterophile immune serum into the carotid toward the heart characteristic symptoms were produced; these were now explained satisfactorily. The same symptoms were obtained by Halber with a heterophile immune serum obtained by injection of the aortic endothelial cells of a horse. When the same serum was injected intravenously, only weak anaphylactic symptoms resulted. These experiments indicated that, in the first place, the heterophile immune serum damages the endothelial cells in the blood vessels.

Primary Serum Toxicity and Anaphylaxis; Differences.—A thorough review of the problem of primary toxicity of heterophile immune rabbit serum for guinea-pigs was made by Redfern in 1926. The manifestations in the guinea-pig following injection were closely similar to those of anaphylaxis. Postmortem observations, however, in animals killed by heterophile immune serum showed different changes from those found in animals that died as a result of a pure anaphylactic reaction. The differences were especially marked in the lungs. In the first group, the lungs were markedly hemorrhagic throughout. There was also a great deal of edema, and the fluid not only filled the lung spaces, but often extended into the trachea and even exuded from the nose. Such a condition was not seen in secondary anaphylaxis. The

edematous lungs were 24.5 per cent heavier than the average weight of anaphylactic lungs.

The study of the action of heterophile rabbit antiserum on the excised uterus of normal guinea-pigs has shown that the uterine muscle from a normal guinea-pig does not behave as does the uterine muscle which has been previously sensitized. The latter responds uniformly to the additions of specific antigen to which it is sensitive. The normal uterus under similar conditions exhibits no such response to the addition of heterophile antibody, although the heterophile antigen has been shown to be contained within the uterine tissue. The reason may be due to the possibility, as shown by Kritchevsky, that the heterophile antigen is contained in the connective tissue of the guinea-pig; therefore the muscle cells do not respond to the heterophile antibody, and it may be that the heterophile antigen is contained within the cells of the uterus and therefore the antibody does not come into intimate enough contact with the antigen.

Local Reactions.—Redfern studied thoroughly the local reactions excited by intracutaneous injections of heterophile rabbit antiserum into normal guinea-pigs. Within a few minutes after the injection, a reaction appeared which was characteristic and due to the presence of the antibody in the injected serum. In guinea-pigs sensitive to the specific protein, general anaphylactic symptoms could be produced, but a local reaction of the character described in his experiments did not occur. The differences were due to quantitative and qualitative conditions in injections of antiserum. In the small quantity injected there was usually a much larger amount of the concentrated antibody, while when antigen was injected into a sensitive animal, a much smaller quantity of the antibody was present in the cells of a small local area. Hence in secondary anaphylaxis the local reaction is not sufficiently strong to cause a violent disturbance and death of cells. It was impossible to demonstrate the toxic substance separate from the heterophile lytic body by fractionation of the antiserum by the use of ammonium sulphate. The cause of death in true anaphylaxis is probably due primarily to the contraction of the smooth musculature of the body, while in primary antiserum toxicity, the rapidly increased permeability of endothelial linings and cell membranes is the most significant factor. This is confirmed by the hemorrhagic and edematous condition in the lungs, the hemorrhagic foci in the skin and the failure of the smooth musculature to contract in vitro.

HETEROPHILE ANAPHYLAXIS

The immunization of rabbits with heterophile organs stimulates the production of an anaphylactic reacting body. It was first shown by Amako, in 1912, that rabbits immunized with emulsions of heterophile

organs become hypersensitive to the injection of sheep cells; the rabbits which he used as controls did not show any reaction. Amako continued to work on the subject and reported his results in 1914. He injected into rabbits the organs of turtles, toads, fish (*Pagrus major*), chickens, oxen, rats, dogs and guinea-pigs and then injected sheep blood. He found the development of a high degree of anaphylaxis, not only for reinjection of sheep blood, but also of goat blood; but there was no reaction after the reinjection of blood from the ox, horse, dog, guinea-pig, turtle and toad. There was no quantitative relation between the hemolytic titer and the degree of anaphylaxis. He has also studied the problem of passive heterophile anaphylaxis in nonimmunized rabbits. Heterophile immune serum was mixed with sheep blood and injected into normal rabbits; all of them showed marked anaphylaxis. Strong anaphylactic symptoms resulted also when the serum was injected into one ear and the blood into another; the same thing happened when goat blood was used instead of sheep blood.

A mixture of heterophile immune serum and blood cells of sheep and goats was kept for an hour at 37 C.; it was then subjected to centrifugalization, washed, and the cells injected into rats. Marked anaphylaxis resulted. When the mixture was kept at room temperature at 0 C., the same result occurred. Heterophile antiserum was mixed with various kinds of blood, both heterophile and nonheterophile; the mixtures were incubated, subjected to centrifugalization and the supernatant fluid separated from the sediment. Then each one was separately injected into rabbits. The supernatant fluid of mixtures with nonheterophile blood cells showed severe reaction when injected into animals and distinct lysis of sheep and goat blood, while those mixed with sheep and goat blood did not produce any reactions or lysis of this blood. Of the animals injected with the sediments, only those which received blood sediments of sheep and goats showed anaphylactic symptoms; the others were inactive. These experiments showed that the reacting body obtained by injected organs was fixed by the blood cells of sheep and goats. Guinea-pigs injected with organs of various animals did not show anaphylactic antibodies against sheep blood.

Relation of Heterophile Anaphylaxis to the Toxicity for Guinea-Pigs.—A distinct parallelism could be observed between the strength of the anaphylactic symptoms, both active and passive, and the degree of toxicity for guinea-pigs. When the serum from immunized rabbits was mixed with sheep blood, it lost its reacting body and also its toxicity for guinea-pigs. The symptoms in the guinea-pigs injected with heterophile serum are due to the antigen contents of their organs. The rabbits do not contain heterophile antigen and show anaphylactic symptoms only when blood from sheep and goats is introduced together with the serum. Taniguchi concluded that the intoxication produced by the

injection of antiserum into suitable animals was due to anaphylaxis. The antigen present in the tissues reacts with the antibody in the injected antiserum. This view is based on the following results: 1. Antiserum containing heterophile antibody produced anaphylactic shock when injected into suitable animals. 2. Heterophile antiserum is toxic only to animals that contain heterophile antigen in their tissues and not to others. 3. The toxicity of heterophile antiserum is removed by contact with heterophile antigen and not with nonheterophile tissues. 4. Organs of animals that do not contain heterophile antigen lack the power to generate toxic antiserum. 5. It is known that animals of the guinea-pig type are incapable of generating the heterophile immune body, and such animals also fail to produce toxic antiserum when injected with heterophile antigens. The author confirms the previous results concerning the discrepancy between the hemolytic titer and the degree of toxicity.

The Toxicity of Horse Serum and of Some Vaccines for Man.—As was shown by Friedemann, normal serum of man and rabbit contains varying amounts of heterophile antish sheep hemolysin, and other authors have found heterophile antigen in horse serum. Therefore the anaphylactic reactions resulting from injections of horse serum into human beings may be due to the interaction of these two substances. As various micro-organisms, especially the Shiga dysentery bacillus, contain heterophile antigen, the reactions resulting from injections of certain vaccines may also be explained in a similar way.

Cellular Anaphylaxis.—Kritchevsky sensitized rabbits with red blood cells of the chicken and then injected them with red blood cells of the sheep; this resulted in severe anaphylactic symptoms. Of twenty-three sheep, twelve died, and the others became extremely sick. These experiments are a strong support to the theory of cellular anaphylaxis. It was contended by others, especially by Friedberger, that anaphylactic phenomena are not due to the cells injected but to traces of serum attached to the cells. In the experiments already described, however, when serum was attached to the cells, it belonged to two species of animals not related. Kritchevsky believed that there is a quantitative relation between the development of the anaphylactic reacting body and the hemolytic titer, stating that whenever the hemolytic titer was not below 0.002 cc. anaphylaxis always was seen, but that when it is below this limit it was seldom observed. Kritchevsky continued the experiments on passive heterophile anaphylaxis. Rabbits were immunized with the blood cells of chickens; their serum was mixed with sheep erythrocytes and injected into normal rabbits, which resulted in severe anaphylaxis in these rabbits. The question of corpuscular heterophile anaphylaxis was again taken up by Hyde in 1926, who stated that it occurred, in his experiments, and that there was no possibility of transferring small amounts of serum.

CLASSIFICATION OF CARRIERS OF HETEROPHILE ANTIGEN

Forssman has already found that the organs of the cat and horse behaved like those of the guinea-pig, while those of the rabbit, ox and rat were not antigenic; neither were yeasts nor *Bacillus typhosus*. Subsequent studies have increased the number of known carriers of heterophile antigen; and numerous other animals and bacteria have been found which are not antigenic and which belong in the rabbit group. Animals classified in the guinea-pig group must fulfil certain requirements. Their organs when injected into rabbits must produce an anti-sheep lysin with all the characteristics of a heterophile immune serum. Furthermore, it must lose its hemolytic titer and toxicity when treated with suspensions of heterophile organs or with sheep cells. The corresponding characteristics are required of bacterial immune serum.

Amako added the turtle, pigeon and dog to the guinea-pig group. Later research has excluded the pigeon from the guinea-pig group as the titer of the lysin produced by its organs was still within the normal limits. Pick and Doerr found a heterophile antigen in the organs of the chicken. Morgenroth added the white mouse and cancer in mice to the guinea-pig group. More recent authors have found that the organs of the white mouse did not behave uniformly, so that some put that animal into the rabbit group; others leave it in the guinea-pig group. Friedberger and Schiff added the eel, frog, goose, organs of the sheep, rabbit, man, rat, ox, hog and pigeon to the rabbit group. Tsuneoka added the gills of carp, pike and tench to the guinea-pig group, while the rabbit group was increased by the addition of mealworms, cockroaches, rice, oats, beans, *Vibrio staeke*, *B. coli*, *B. tuberculosis*, staphylococci, bran and champignon. Amako obtained rather indefinite results with the organs of toads and of a fish (*Pagrus major*). Gaethgens added the whale and camel to the guinea-pig group, the herring, codfish and shellfish to the rabbit group. Sordelli, Fisher, Wernicke and Pico added the species *Cavia aperea* to the guinea-pig group. Meyer found that the tapeworm is nonheterophile in type. An important step forward was made when Jijima added the Shiga dysentery bacillus to the guinea-pig group while the *Vibrio cholerae*, *B. typhosus*, *B. paratyphosus* B, and *B. enteritidis* Gaertner were placed in the rabbit group.

In 1913, Friedberger and Schiff reported the production of an anti-sheep lysin in rabbits by the injection of human blood. The titer for the blood of sheep was higher than for human blood. This observation became of especial interest when Schiff found the presence of heterophile antigen in human red blood cells belonging to Jansky's groups 2 and 4 (receptor A and A plus B).

When Rothacker reported the observation of heterophile antigen in a mixture of *B. paratyphosus* B and *B. enteritidis* Gaertner, a long discussion started on that subject. Tsuneoka did not find heterophile

antigen in the same organisms. Some of the later investigators were not in accord with Rothacker. The only micro-organism which was found to have heterophile antigen was the Shiga dysentery bacillus. Antisheep lysin produced by injecting rabbits with Shiga bacilli was completely absorbed by suspensions of heterophile organs, while Shiga bacilli absorbed only a small amount of antibodies from other heterophile immune serums. This discrepancy is explained by the assumption of various partial antigens of which the Shiga bacilli contain a much smaller number than the organs of animals of the guinea-pig type. The Shiga immune serum is only slightly toxic for guinea-pigs. This also may be explained by the same hypothesis (Jijima and Fujita). Schmidt thought that the action of the Shiga bacilli was not specific, while Meyer agreed with the Japanese authors. The last addition to the micro-organisms containing heterophile antigen was that of Powell, who found it in one of twelve strains of *B. leptisepticum*. He did not find it in the three strains of the hemorrhagic septicemia group of organisms isolated from guinea-pigs, in the one strain of *B. avisepticus* or in the three strains of *B. bronchisepticus*.

DISTRIBUTION OF HETEROPHILE ANTIGENS IN VARIOUS ORGANS

The different organs of the animals belonging to the guinea-pig group contain varying amounts of heterophile antigen. According to Amako, the kidney of the turtle has only a little antigen, while the brain, liver and spleen are rich in it. Pick made an interesting observation showing the presence of heterophile antigen in the lenses of animals of the guinea-pig type. The immune serum produced by injection of lens substance does not produce cataracts when injected into guinea-pigs. It seems that aging (cataract formation) increases the antigenic quality of the lenses. While the red blood cells of the guinea-pig are not antigenic, its serum contains heterophile antigen (Orudschiew). The leukocytes of the guinea-pig are also able to produce a heterophile anti-sheep hemolysin (Spaet). In most of the animals, the lungs, heart, muscle and kidneys are more antigenic than the liver and brain. Doerr and Pick formulated a law according to which animals whose organs are antigenic do not contain heterophile antigen in their red blood cells and vice versa (sheep and goats contain heterophile antigen in their red blood corpuscles but not in the organs; the guinea-pig and other animals of its type contain it in their organs and not in their blood). That law lost its validity when Kritchevsky showed the presence of heterophile antigen in the red blood corpuscles of the chicken, the organs of which contain heterophile antigen. Kritchevsky agrees with Bail and Margulies, who think that the connective tissue is the site of the heterophile antigen. The presence of the heterophile antigen in the endothelial cells of the aorta helped to clarify a number of contradictory observations

(Halber). The presence of heterophile antigen in the urine of guinea-pigs was observed by Doerr and later confirmed by Friedberger and Schiff. Friedberger and Suto found it in the urine of horses.

The Rôle of Connective Tissue and of Serum.—Bail and Margulies studied the relation of the serum to the antigenic qualities of tissues, and concluded that if organ emulsions of heterophile animals are treated with the serum of nonheterophile animals, they lose the antigenic qualities. They found that a certain relation has to be maintained between the quantity of the organ emulsion and the amount of the serum. The ability to bind heterophile antibodies was tried. Boiling restored the binding ability which was lost due to the admixture of serum of nonheterophile animals. The second phase of the question, whether a mixture of serum of heterophile animals would impart antigenic qualities on nonheterophile tissue, was studied, but a definite conclusion was not reached. The conception of Bail and Margulies is that every animal possesses antigenic qualities, as the connective tissues have the same character everywhere; the apparent lack of antigenic qualities is due to the serum mixed with the organs. Their results were not confirmed by Kritchevsky. Friedemann explained the results of Bail and Margulies by the presence of normal antisheep hemolysin heterophile in type in animals of the rabbit group. He thinks that normal hemolysin is able to combine with the antigen in the organs.

HETEROPHILE ANTIGENS IN TUMORS

The contents of tumors in heterophile antigen was first studied by Pick and Doerr, whose results were not uniform. Morgenroth found heterophile antigen in mice with cancer. The highest titer was 0.0005 cc. and 0.00025 cc. The heterophile immune serum produced by tumor cells is the same as the one produced by normal organs. Their results were confirmed by Sordelli, Fisher and Wernicke. One can assume at present that if an organ contains heterophile antigen, tumors originating from it will also be antigenic.

NORMAL ANTISHEEP HEMOLYSIN IN RABBITS

The production of heterophile antibodies is intimately connected with the normal antisheep lysin in the animals of the rabbit type. Friedberger and Schiff studied the presence of normal antisheep lysin in seventy rabbits, using 0.1 cc. of guinea-pig complement. The lowest titer was 0.2 in thirty-two, the highest 0.02 in two of the animals. They noticed that the lower the normal lysin, the higher was the increase after immunization. Friedemann and others have analyzed the normal anti-sheep lysin and found that it is heterophile in character. Friedemann concluded that animals of the rabbit type contain natural antisheep lysin, while those of the guinea-pig type contain none or only isophile amboceptors.

Origin of Normal Heterophile Antibodies.—Friedemann has suggested an ingenious hypothesis to explain the origin of the normal heterophile amboceptors. Primarily the organs of all animals contain heterophile antigen. In the later development, as a response to the antigens, antibodies are developed. In some cases in which there is a surplus of antigen and only a weak antibody production, conditions will result as they are found in the guinea-pig, cat, dog and horse, but when the antibody production is strong and the heterophile antigen is scanty, the latter will not be demonstrable, and as a result the conditions will be as in the rabbit, man and the hog. Rubinstein only partly confirmed the results of Friedemann.

Heterophile Antigen in Embryonal Tissues.—In view of Friedemann's hypothesis, the study of antigenic qualities of embryos is of importance. Tsuneoka found that they possessed antigenic qualities identical with those of the organs of corresponding adult animals. Kritchevsky found that hen's eggs do not contain heterophile antigen even when injections are made with hen's egg containing a formative yolk. Rabbits were injected with chicken embryos of different ages: 2, 4, 6 and 11 days. Heterophile antigen does not appear in the embryo earlier than four days after the division of the egg has begun. After two days, the protoplasm of the embryo does not possess heterophile sheep antigen.

HETEROPHILE AGGLUTININS

The early workers on heterophile antibodies considered it a characteristic feature of heterophile immune serum that it does not contain heterophile agglutinins (Doerr and Pick). Their presence was first proved by Fukuhara and Ando, who injected rabbits with various kinds of blood and heterophile organs and obtained heterophile agglutinins for *B. typhosus*, *B. paratyphosus* B, *B. psittacosis*, the bacilli of mice typhoid, and of swine plague, and Danysz's bacillus with injections of the liver and kidneys of guinea-pigs. Normal agglutinin titer was from 1:1 to 1:5; after the immunization it became from 1:200 to 1:800. There was no increase of agglutinins for *Vibrio* of cholera, *B. coli*, *B. paratyphosus* A, *B. enteritidis* Gaertner, *B. dysenteriae* Flexner, *B. mutabilis*, *B. pyocyaneus*, *B. alcaligenes* and the bacillus of cholera in chickens. Kritchevsky found high agglutination for the red corpuscles of the hen and of the sheep in rabbits immunized with hen's blood. The heterophile agglutinin developed to a lesser degree than the lysin. An interesting observation was made by Trou-Hia-Hsu, who showed the presence of specific agglutinin for sheep erythrocytes in heterophile immune serum only when erythrocytes a few days old were used. The heterophile agglutination is specific both as to serum and

antigen; that is, another amboceptor, for instance an ox amboceptor, does not act on old sheep erythrocytes; nor does the heterophile immune serum of sheep act on other blood corpuscles, for instance on old ox blood. The agglutination begins after the blood cells are from 2 to 3 days old, and it is not due to the presence of bacteria in the suspension nor to the suspending fluid, as agglutination is not observed when fresh sheep erythrocytes are suspended in the fluid taken from an old suspension. Old sheep cells were agglutinated also. Treatment of sheep erythrocytes with heat, alcohol, ether or osmic acid did not make them agglutinable. The heterophile agglutinin is fixed by fresh, old and boiled sheep erythrocytes and also by the kidneys of guinea-pigs.

Friede and Gruenbaum found heterophile agglutinins for cat erythrocytes in rabbits immunized with the blood of sheep, while these erythrocytes produced a large amount of isophile agglutinin but no heterophile agglutinin for sheep blood. In this connection it is of interest that Langer noticed a marked increase of agglutinins in rabbits by daily repeated venesections. In some of the animals titers were increased up to 250 times the original. Klinger and Landau could not confirm this result. In a series of experiments repeated by Langer, he again found an increase of agglutinins with the same method, although it was not so marked as at first. Olsen repeated these experiments, with negative results. Ballner and Sagasser, by injecting rabbits with rose yeast, produced agglutinins for *B. typhosus*, *B. dysenteriae* and *B. coli*. Cohn produced an increase of agglutinins for *B. typhosus*, *B. paratyphosus* A and B, and *B. dysenteriae* Flexner up to from 1:400 to 1:800 with injections of yeast, while the original titer was only 1:20. The results, however, were not uniform. Kolmer and Toyama found that arsphenamine and mercuric chloride in small doses increased the production of agglutinins for erythrocytes and *B. typhosus*.

HETEROPHILE PRECIPITINS

Friedberger and Collier produced heterophile precipitins for the protein of sheep by injecting rabbits with the serum of horses. In some cases the reaction with the protein of sheep was stronger than with the protein of horses. The heterophile precipitins could be removed by treating immune serum with the blood of sheep and when the serum was diluted the precipitins lost their effect. The results were not uniform, and were not confirmed by Neumarck, Manteufel and Beger. They emphasized especially that heterophile precipitation was always weaker than the isophile. The report of obtaining antidog serum by injection of a rabbit with the serum of a dog was interesting. The serum precipitated dog serum up to 1:20,000 and the serum of the horse and donkey in the same dilution. It was later found that the dog had been fed with horse meat for many years. It was not possible to demonstrate

horse antigen in the serum of the dog by precipitation but was assumed that there was a relation between the horse and donkey precipitins and the food (Friedberger and Jarre).

MORPHOLOGY AND CHEMISTRY OF HETEROPHILE PRECIPITATES

The morphology of the isophile and heterophile precipitates was thoroughly studied by Friedberger and Meissner. They had an anti-horse serum which precipitated in almost the same intensity (titer 1:20,000) the serum of cows, deer, goats, pigs, sheep and man. The isophile precipitates are gray, consisting of loose, coarse flocculi. The fluid between the flocculi is cloudy. The heterophile precipitates are whitish, consisting of dense and fine flocculi. The fluid between the flocculi is clear. The precipitates of related species show a mixture of both types with prevalence of the loose type. Absorption experiments showed that the isophile antigen removes both the isophile and the heterophile precipitins while the heterophile antigen removes the heterophile precipitins and makes the immune serum in this way more specific. According to Friedberger and Lassnitzki the isophile precipitates are protein in nature while the heterophile are lipoidal.

Meissner examined seventy-eight antisera and found that 55.8 per cent were absolutely specific or reacted only with the next related proteins, that 44.2 per cent showed a heterophile reaction, and that 11.7 per cent of the latter reacted with heterophile antigen in the same dilution as with the isophile. There was not any relation between the nutrition and the sex and the production of heterophile precipitins. The season of the year seemed to be of some influence, as between November and March the frequency of nonspecific serum was higher than between April and October. Smaller (younger) animals produced more frequently heterophile precipitating serum than larger (older) ones.

HETEROPHILE COMPLEMENT FIXATION

It has long been known that rabbit serum along with emulsions of alcoholic extracts of tissue frequently fixed the complement. This property was roughly but not always parallel with the contents of the normal sheep hemolysin which is heterophile in type. It was shown by Taniguchi that with the development of heterophile sheep lysin there was a parallel development of the capacity for fixing the complement in the presence of alcoholic extract. With extracts of heterophile organs much more complement was fixed than with other extracts. After the serum containing heterophile antibody was deprived of the hemolytic immune body by digestion with heterophile antigens, it lost a greater part of the complement fixing ability with heterophile organ extracts, but still fixed a certain amount and practically an equal amount with

nonheterophile organs. When the immune serum was mixed with suspensions of nonheterophile tissues the complement fixing ability remained unchanged. There was, according to this author, a distinct quantitative parallelism between the hemolytic and the complement fixing properties of heterophile antiserum. The complement fixation occurred both in the ice chest and at 37 C. Turbid lipoid emulsions fixed more complement than clear ones. Addition of cholesterol acted in the same sense. Georgi also found that antish sheep lysin of rabbits fixed the complement with an extract of beef heart, but to a much lesser degree than with an extract of guinea-pig heart. The antiserum itself did not have an anticomplementary action, but when alcohol itself was used instead of the extract there was a distinct anticomplementary action. Therefore, when there was an apparent fixation of the complement with the beef heart extract this might have been due to the anticomplementary influence of the alcohol.

The Possibility of an Error in the Wassermann Reaction.—Georgi pointed out the possibility of a nonspecific reaction resulting from the presence of heterophile antigen in the hearts of horses and guinea-pigs in case the latter should be used for the preparation of antigens. The heterophile antigen may react with the normal antish sheep lysin in human serum. This possibility was again analyzed by Taniguchi who used a human serum that gave a weakly positive Wassermann reaction with alcoholic human or ox heart antigens and which was rich in natural sheep hemolysin (titer 0.003 cc. for 0.5 cc. of 3 per cent sheep blood suspension with 0.05 cc. of guinea-pig complement). The test was repeated with alcoholic extract of guinea-pig heart as antigen and more than five times as much complement was fixed as in the previous test. As a control, another weakly positive serum with practically no sheep hemolysin was used. The same amount of complement was fixed with all three antigens. A negative serum which contained sheep hemolysin fixed twice as much complement with guinea-pig heart as with ox heart extract. Similar results were reported by Meyer who also emphasized the possibility of obtaining false positive precipitation reactions. The latter possibility was also studied by Hooker.

Normal Antish sheep Hemolysin in Human Serum.—Taniguchi found six of 134 human serums to be rich in sheep hemolysin. It had all the characteristics of a heterophile lysin.

THERMOSTABILITY OF HETEROPHILE ANTIGENS

The heterophile antigens show a high degree of thermostability. Amako found that the higher the temperature the more the antigenic power is affected, and at 100 C. it is destroyed almost completely. This result was corrected by later research. Pick and Doerr observed the high resistance of heterophile antigen to protein coagulants such as heat

and alcohol. When boiled even for a long time, the antigen was able to produce in the rabbit an antish sheep lysin and toxic substances for guinea-pigs as well as to fix the complement in vitro. This was confirmed by Bail and Margulies and by Sachs and Nathan. It was known that rabbits injected with sheep blood also produce an antiox lysin. Sachs and Nathan observed that the blood of sheep loses its ox antigenic quality on boiling. Forssman and Bang found that boiling does not destroy the ox hemolytic antigen in ox blood. Forssman studied the question whether the antigen receptors which produce identically acting antibodies are identical or not. He found that when sheep cells were boiled at 100 C. for one-half hour they lost the ox antigen, still retaining goat and sheep antigens. The same happened when they were heated for one-half hour at 110 C. and 120 C. and also when the sheep cells were boiled for one hour at 100 C. in a hundredth-normal solution of sodium hydroxide. When they were boiled for one hour at 100 C. in a tenth-normal solution of sodium hydroxide, all antigens were destroyed. It was impossible to separate the sheep and the goat hemolytic antigens. Goat's blood was treated in a similar way. The sheep and goat antigens in it could not be separated by heating up to 130 C. The ox antigen in goat blood, however, is more resistant to heat than in sheep blood as it stands heating in the autoclave up to 110 C. for one-half hour, becoming only slightly weaker, and is completely destroyed at 120 C. The ox antigen in ox blood is not damaged even by heating to 120 C., thus behaving differently from the ox hemolytic antigen in sheep blood. The sheep and goat hemolytic antigen in ox blood proved not to be resistant to heat. Thus the sheep and the goat antigens in sheep and goats stand 120 C. for one-half hour, while they are destroyed at 100 C. in ox blood; the ox hemolytic antigens in ox blood are not destroyed by 120 C. for one-half hour. In goat blood it is destroyed by 120 C. for one-half hour, but not by 110 C. for one-half hour, while in sheep blood it cannot stand 100 C. for one-half hour. The sheep and goat antigens in the organs of guinea-pigs behave in the same way as the same antigens in sheep blood. These results justify the conclusion that antigens acting identically but showing different resistance to heat are not identical. Gutfeld used higher temperatures up to 200 C. in studying the thermostability of antigens. One hundred and twenty degrees centigrade did not reduce the antigenic ability, but heating for fifteen minutes at from 160 C. to 180 C. and 200 C. removed entirely the antigenic quality of the blood of sheep. Horse kidney was more resistant. Its heterophile antigen was not influenced by heating at 200 C. for fifteen minutes. It was impaired after thirty minutes and destroyed completely after sixty minutes. Landsteiner observed that a horse kidney lost its heterophile antigen when extracted with alcohol and heated during the

extraction. It seems that boiling alcohol destroys completely the antigenic quality while boiling water does not.

Thermostability of Heterophile Antibodies.—Gutfeld found that heating heterophile serum for fifteen minutes at 62 C. made no change, fifteen minutes at 65 C. diminished its hemolytic function and five minutes at 70 C. removed its function. According to Friedberger and his school, antibodies fixed by the antigen are thermostabile. Gutfeld, however, found that the heterophile amboceptor fixed by fresh sheep blood was completely destroyed by heat at 70 C. for ten minutes. His experiments proved that the complementophile and probably also the cytophile group of the amboceptor were destroyed by heating.

The Two Receptors in Erythrocytes of Sheep.—The absorption of heterophile immune serum obtained by injection of rabbits with sheep cells, fresh or boiled, and with heterophile organs show conclusively that the sheep cells contain two antigens: one is thermostabile, of similar character as the heterophile antigen in organs of animals belonging to the guinea-pig type; the other is destroyed by heat and is responsible for the production of the isophile fraction of the antiserum. The former was removed by absorption with heterophile serum, boiled and fresh sheep blood cells, the latter only by fresh sheep blood cells. The amount of both kinds of antibodies produced by the blood cells of sheep varied in different serums. The amount of heterophile antisheep lysin was largest after a single injection (Orudschiew).

HETEROPHILE IMMUNIZATION BY MOUTH

Powell obtained antisheep lysin by feeding rabbits with heterophile antigen. The antigens used were red blood cells of the hen, sheep and goat, the kidneys of horses and guinea-pigs and liver. Control rabbits were fed with nonheterophile tissues. The highest titer obtained was 4,000 units. The unit of hemolysin was the amount which in one hour at 37 C. laked 1 cc. of a 1:4 dilution (in terms of whole blood) of washed sheep blood cells with 0.1 cc. of a 1:5 dilution of guinea-pig complement. The antibodies so produced were heterophile in character. Only a few rabbits yielded also a small amount of isophile antibody. The serum was toxic for guinea-pigs.

THE CHEMICAL NATURE OF HETEROPHILE ANTIGENS

One of the first attempts to define the chemical nature of the heterophile antigen was that by Amako. He extracted the organs of guinea-pigs with 95 per cent alcohol to see if the extracts were antigenic. He injected the extracts into rabbits with negative results. Friedberger and Schiff extracted the urine of guinea-pigs with alcohol, and only the extract but not the sediment was antigenic. The alcoholic extract

could be divided into two fractions, when treated with colloidal ferri-oxychloride. Only the filtrate was antigenic. Roerr and Pick came to the conclusion that the heterophile antigen was chemically a nucleoprotein, but was not necessarily found only in nuclei.

Their Lipoidal Nature.—Sordelli, Fisher, Wernicke and Pico isolated from an alcoholic extract of horse kidney, treated with acetone, ether and benzol, a substance able to fix heterophile hemolysin. The isolated substance had no antigenic qualities. The organs extracted had still some antigenic power but could not bind antibodies. From the isolated substance a cerebroside was obtained $\frac{2}{100}$ of a mg. of which fixed 50 hemolytic units of a heterophile lysin. Sphingomyelin was found inactive. Friedberger and Suto extracted heterophile antigen in horse urine with alcohol. The extract was antigenic, producing a heterophile lysin while the alcohol insoluble fraction did not show any antigenic properties. The alcoholic extract was further precipitated with phosphoric-tungstic acid. Only the filtrate showed antigenic qualities producing a lysin while the precipitate was not antigenic. The alcoholic extract was treated also with colloidal ferri-oxychlorid but none of the fractions so obtained were antigenic. Taniguchi found that alcohol soluble and acetone insoluble constituents (lecithins) of heterophile organ extracts fix the antishoop heterophile antibody produced in the rabbits. Extracts of organs lacking the heterophile antigen do not fix heterophile antibody.

Niederhoff injected rabbits with the alcoholic lipid extract of guinea-pig kidneys but hemolysins were not produced. Schmidt, after a series of rather complicated experiments, came to the conclusion that there are two antigenic substances in the blood cells of sheep, one a protein which cannot stand heat, the other a lipid which is the heterophile resistant antigen. Gutfeld extracted heterophile organs with sodium hydroxide, hydrochloric acid or alcohol, and the extracts had the ability to fix heterophile antibody but not the isophile. This fixation was not due to the antilytic action of the solution. Sordelli and Fisher found that the alcoholic extracts of heterophile antiserum were able to fix the complement. This was confirmed by Meyer. The acetone insoluble fraction is the one containing the antigenic portion. The lipid extract did not produce antibodies when injected into rabbits.

The Hapten Hypothesis.—An important contribution to the heterophile problem was made by Landsteiner in 1921. His experiments were carried out to a great extent before he knew of Sordelli's work, and his results were similar to those obtained by Sordelli and his co-workers. He also found that the alcoholic and ether extracts of heterophile organs fixed the heterophile antibody in vitro but could not produce antibodies, while the alcohol precipitate had immunizing but

no fixing abilities. Landsteiner suggests the hypothesis that the antigen consists of a protein fraction necessary for immunization and of a probably lipoid fraction attached to the former, which contains the specific binding group; the latter can be extracted with alcohol and partly with ether. Landsteiner calls those specifically binding and not immunizing substances, haptens.

Reactivation of the Hapten.—Landsteiner, as the first to reactivate the hapten by mixing the alcoholic extract with diluted hog serum and by injecting the mixture into a rabbit, also succeeded in obtaining a lysin for the blood of sheep. Georgi was not able to reactivate the hapten with a watery extract of rabbits' kidneys or horse serum. Landsteiner and Simms reported reactivation of the hapten with pig and human serums. Such mixtures are considerably more active than the same substances injected separately; accordingly the effect is probably due to the formation in vitro of a loose compound between the alcohol soluble substances and a protein, the compound acting as a complete antigen. The results of Landsteiner and Simms were checked by Takenomata, who obtained a powerful heterophile lysin by injecting rabbits with a mixture of alcoholic extract of horse kidney and hog serum. The highest titer reached was 0.0003 cc. using 0.25 cc. of 1:10 dilution of guinea-pig complement and 0.25 cc. of sheep cells. The immune serum precipitated alcoholic extracts of heterophile organs, and fixed complement in the presence of the latter. There was a marked precipitin production for hog serum which was out of proportion to the small quantity of serum used for the immunization. Control experiments carried out with injections of alcoholic horse kidneys alone were not successful, but the same rabbits responded to a mixture of extracts and serum with antibody production. Injection of hog serum alone was not as successful as the injection of beef kidney extract and hog serum.

In the experiments of Heiman reactivation of the hapten was accomplished much better with hog serum than with horse serum. When horse serum was used, more injections were necessary for the same purpose. I confirmed the results obtained by Sachs, Klopstock and Weil, who produced antibodies by immunizing rabbits with a mixture of lecithin and hog serum and of cholesterol and hog serum. The hog serum was more efficient than the horse serum. The better effect of the horse serum in combination with the organ extracts is not due to a higher production of homologous precipitins by the horse serum than by the hog serum because the difference in that respect is only slight. Doerr and Hallauer reactivated the hapten successfully with beef and human serum, bacterial proteins and with watery extracts of rabbit organs. The latter makes it improbable that the activating ability depends on the antigenic quality. The rabbits so immunized develop two different antibodies:

Forssman's amboceptor and a precipitin for the heterologous protein. These are entirely independent of each other and can be removed separately from the immune serum by specific fixation with the corresponding antigen. The two components form probably a physical combination and it may be that the so-called activator (serum, watery extracts of organs) surrounds the lipoidal hapten particles. The activating proteins must be finely dispersed (in a colloidal solution), so as to be able to combine in vitro with the lipid. I used as activator intact and laked erythrocytes, in order to show this. According to this conception only laked corpuscles should act as activators, as shown by the experiments. One experiment was successful even when the erythrocytes of rabbits were used. Later, Doerr and Hallauer reported that *B. typhosus*, *B. coli*, *Micrococcus roseus*, rose yeast and other organisms were effective either alive or killed. *B. subtilis*, *B. mycoides* and other spore forming saprophytes as well as their vegetative forms did not activate Forssman's antigen. Lipoid and bacteria had to be mixed in vitro before the injection. If injected separately the result was negative. The hapten was injected into rabbits infected with bacteria, assuming that from the infected foci bacterial proteins are constantly absorbed which may activate the hapten. The results were negative. The reactivation of the hapten by ultraviolet light was not possible. Bacterial proteins were used successfully for reactivation of the hapten by Mera.

Taniguchi observed that tissues which were extracted with alcohol for forty days showed complete absence of the antibody fixing ability. An extraction period of from seven to ten days did not destroy this ability, although the coagulation of the protein was complete. The disappearance of the power to fix after a prolonged extraction is therefore not due to the coagulation of the proteins but to the removal of the lipoids.

Mizuhara treated alcoholic extract of guinea-pig heart with cobra venom whose active principle is a lecithinase which destroyed the property of the guinea-pig heart extract to fix the complement with heterophile serum, showing the lipoid nature of the heterophile antigen.

Chemical Analysis of the Active Principle in the Heterophile Antigen.—Landsteiner and Levene made a thorough chemical analysis of the active principle in heterophile antigen. Fractions of different chemical compositions, as regards their nitrogen, phosphorus and sulphur, were approximately of the same activity. It is possible that in the organ extracts the activity of the specific substance is enhanced by other substances, in themselves inactive. These investigations succeeded in increasing the strength of alcoholic extracts of horse kidneys by adding to them crude sphingomyelin of ox brain, which in itself has hardly any activity in tests with heterophile antibodies. The active fractions were quite soluble in water giving a clear solution; they were

insoluble in ether, alcohol, acetone and chloroform. The solution gave a negative biuret test. Two samples were analyzed; the composition calculated for the ash free substance was as follows:

Carbon	59.64
	58.98
Hydrogen	10.09
	9.44
Nitrogen	2.33
	2.33
Phosphorus	1.19
	0.90
Sulphur	0.81
	0.51
Ash	4.22
	4.03

On hydrolysis with hydrochloric acid, the product yielded water insoluble acids and a reducing substance which gave with orcein the color test for galactose. It did not reduce Fehling's solution directly but did so after hydrolysis in hydrochloric acid.

Immunization Experiments with Lecithin and Cholesterol.—Recently Levene, Landsteiner and Van der Scheer reported the results of immunization with lecithin. They are a check on the results by Sachs and Klopstock, who succeeded in obtaining antibodies by injecting rabbits with emulsions of lecithin or cholesterol containing pig serum. There are, however, some contradictions in the results of Sachs and Klopstock. Their antilecithin serum reacted with lecithin Merck, but it also reacted with cholesterol and even stronger than with lecithin. This was attributed to the presence of cholesterol in the lecithin used. Furthermore, the purer of the lecithin preparations was the less active. Heiman confirmed these results. He noticed that the lecithin antibodies could be detected easier when cholesterol was added to the lecithin in the complement-fixation test. Levene, Landsteiner and van der Scheer repeated these experiments and their results were identical when commercial egg lecithin Merck was used. The other results were rather contradictory. One of the preparations produced a serum which reacted in complement fixation and flocculation tests with another lecithin preparation but not with itself. Another reacted with cholesterol, although the latter was not present in the injected material. There is a possibility that the active agent producing the antibody is not lecithin itself but some other substance present in the lecithin preparation.

The Chemical Nature of Heterophile Antibodies.—Little attention has been paid to the chemical nature of the heterophile antibodies. Friedberger and Goretti dialyzed and precipitated heterophile immune serum with carbonic acid and separated the globulin and albumin fraction. The globulin fraction contained the bulk of the amboceptor but lacked toxicity which was present in the albumin fraction.

HETEROPHILE PRECIPITATION REACTION

To Sordelli and Pico credit is due for having discovered, in 1919, the precipitation reaction that occurs when a heterophile lysin for sheep or goat corpuscles is added to an alcoholic extract of a heterophile tissue suspended in a salt solution. They consider this phenomenon a reaction between the antibody and heterophile antigen. It does not occur in the absence of sodium chloride. Complement fixation tests showed that the amboceptor is attached to the floccules of the precipitate.

Practical Application for the Recognition of Horse Meat in Foodstuffs.—Sachs and Guth reported identical observations in 1920. They mixed an alcoholic extract of horse meat with a serum containing heterophile antibodies and obtained a precipitate. They suggested that this reaction be used as a means of detecting horse meat in foodstuffs, to replace the older procedure of Sachs and Georgi in which the complement fixation test was used for the same purpose. Horse meat belongs to the heterophile guinea-pig group and is able to absorb the amboceptor from the heterophile antisheep immune serum of the rabbit. The material suspected to contain horse meat is mixed with a heterophile immune serum and if the latter shows a decrease of its amboceptor in a hemolytic test, the material tested must contain horse meat since beef, pork or sheep belong to the rabbit group and cannot fix the amboceptor. The particular advantage of this method is that the heterophile antigen of the horse meat is not influenced by boiling while the formerly used biologic tests for horse meat could not be carried out after the meat was boiled.

Analysis of the Precipitate.—Schmidt extracted the flocculi of the precipitate with lipoid solvents and so recovered the heterophile antigen which gave again a precipitate with the heterophile rabbit serum. These observations were confirmed by Taniguchi who concluded that the precipitation never occurred when heterophile antiserum and lipoid emulsion of nonheterophile tissues or nonheterophile serum and lipoid emulsion of heterophile tissues were mixed. Heterophile antiserum is deprived of its precipitating power by digestion with suspensions of heterophile tissues but not of nonheterophile tissues. The alcoholic extract of the precipitate has the same qualities, as far as complement fixation is concerned, as the original alcoholic extract, but the supernatant fluid does not show any of these qualities. The analysis of the

floculi resulting from the reaction between the alcoholic extract of heterophile organs and the immune serum showed that they contain 80 per cent lipoids (Schmidt). By proper procedure (treatment with sodium hydroxide) the lysin could be separated from them. This makes it probable that during the heterophile precipitation reaction a primary fixation occurs (chemical or absorptive electrical) between the immune serum and the organ lipoids. The colloid changes then produce flocculation.

Fornet first noticed a double ring in precipitation reactions. This phenomenon was rediscovered in 1925, by Friedberger and Ikeda, who observed the formation of two rings in precipitation tests for serum. The upper consists of fine floccules which are to a great extent soluble in ether and turn black under the action of osmic acid and red under the action of sudan 3. They correspond to the type of precipitate in the precipitation of heterophile antiserum and antigen, as described by Friedberger and Meissner. The lower ring consists of heavy floccules which are not lipoid and correspond to the type of precipitate observed in nonheterophile precipitation. The formation of the upper ring can be prevented by treating the serum with any boiled protein; the upper ring is due to a lipoid-antilipoid reaction, the lower to a protein-antiprotein reaction. If antigen and antibody or antigen itself are extracted with ether, only the lower (protein-antiprotein ring) is formed.

MULTIPLICITY OF HETEROPHILE ANTIGENS

Friedberger and Schiff succeeded in 1913 to produce an antisheep lysin in guinea-pigs by the injection of the boiled sheep cells. This was rather a paradox as guinea-pig organs are able to fix the heterophile antisheep lysin produced in rabbits by the injection of the boiled blood cells of sheep. The lysin so produced was weak (0.04 to 0.06 cc.). The result was confirmed by Weil, who obtained even a higher titer (0.005 cc., being ten times the normal amount). The lysin was not fixed by the organs of the guinea-pig *in vitro* and did not show toxicity for guinea-pigs. It is apparent, therefore, that the antigen contained in the boiled sheep cells is not identical with the one in the organ cells. In Weil's experiments the lysin obtained in guinea-pigs was not fixed by the boiled sheep blood cells and heterophile organs. Forssman and Fex repeated the same experiments and obtained a still higher lysin (0.001 cc. for sheep blood and 0.003 cc. for goat blood). Tsuneoka immunized a dog with the boiled sheep blood and obtained an anti-sheep lysin which was fixed by a suspension of dog kidney. This would indicate that when a lysin is fixed by an organ it still does not exclude its production in the corresponding animal. Only if the antigen is present in the circulation of the animal (endothelial cells or red blood cells) the injection of an identical antigen will not produce antibodies.

Schmidt observed that when a heterophile immune serum is precipitated with the alcoholic extract of the organs of the guinea-pig, the supernatant fluid, after being subjected to centrifugalization, precipitates again extracts of other organs of the guinea-pig with the exception of the one used for the first precipitation and organ extracts of other animals of the guinea-pig type. This observation pointed to a difference in the antigen in the various organs of the same animals and of different animals. Kritchevsky and his associates gave particular attention to the question of multiplicity of heterophile antigens. As discussed previously, he discovered the presence of the heterophile sheep antigen in chicken erythrocytes. Later he reported the presence of a heterophile antigen for chicken erythrocytes in sheep blood. The heterophile chicken lysin has a structure similar to the heterophile sheep lysin. Rabbits immunized with sheep blood do not show heterophile anaphylactic symptoms when reinjected with chicken blood, while when treated with chicken blood they are sensitized for sheep blood. Kritchevsky concludes that the animal cells contain (1) isophile receptors, (2) receptors of phylogenetic related species and (3) heterophile receptors of phylogenetic, not related species. By the immunization of animals three kinds of antibodies can be produced: (1) isophile, (2) those that are against related species and (3) heterophile. Accordingly, the conception of the specificity of antibodies must be revised.

Fujita in his studies of the heterophile antigen and the Shiga dysentery bacilli wondered, as others before had, why the corresponding immune serum has hardly any toxicity for guinea-pigs, which is in variance with the properties of other heterophile immune serums. To explain it, he assumed that heterophile organs had a number of partial Forssman antigens of which only a small fraction is contained in the Shiga bacilli. This may explain why the Shiga antiserum is so well stood by guinea-pigs.

Friede and Gruenbaum found another heterophile antigen in sheep erythrocytes—for cat blood cells and vice versa, a heterophile sheep blood antigen in the erythrocytes of the cat. In the immune serum of rabbits injected with sheep blood, there are, besides isophile, also heterophile agglutinins for cat erythrocytes while cat erythrocytes produce a large amount of isophile agglutinins in rabbits but do not produce any heterophile agglutinins for sheep blood. A small amount of isophile lysins are produced by cat blood.

Friede found that normal rabbit serum did not contain lysins for the red cells of the tortoise, but that sheep erythrocytes contain a heterophile tortoise antigen. Rabbits immunized with tortoise erythrocytes developed a lysin for sheep cells (dilution 1:500 to 1:1,000) which was much stronger than the isophile lysin for tortoise blood (lysin incomplete even in dilution 1:100). The low hemolytic titer for tortoise

blood may be due partly to a high resistance of tortoise erythrocytes to lytic influences or even to chemicals, and to the fact that the complement used was from a warm blooded animal. Chicken erythrocytes contain a heterophile tortoise antigen and tortoise erythrocytes contain chicken antigen. The kidneys of the cat contain a heterophile chicken and tortoise antigen and the same was found to be true of the kidneys of guinea-pigs and horses. The antigenic properties are much weaker in all of those organs for tortoise corpuscles than for sheep and chicken. Friede thinks that, in addition, animal cells contain other antigenic complexes. Here may be a promising task for future workers.

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Notes and News

Italian Congress of Legal Medicine.—The third national congress of legal medicine was held in Florence recently. In addition to a large number of papers on various subjects, the following principal topics were discussed: legal medicine in Italy during the past ten years; the importance of the constitutional factor in the causation and settlement of industrial accidents; acute poisoning from carbon monoxide, and legal medicine in relation to a scientific police system. The next congress will be held in Bologna in 1929.

Registry of Bladder Tumors.—The American Urological Association has established a registry of bladder tumors, and requests the medical profession to cooperate by registering cases of these tumors with the curator of the Army Medical Museum, Washington, D. C., who will furnish blanks for the reporting of cases and answer any correspondence in reference to the registry.

The purpose of the registry is (a) to define the pathologic entities, (b) to determine the course of the pathologic processes and (c) to determine what methods of treatment yield the best results.

The cases of most importance from the standpoint of the registry are those in living persons that can be recorded and followed throughout the course of the disease; the registry is primarily concerned with this class. Any case in which the patient is living and in which the physician has complete data with reference to the history and operative or other treatment, is valuable for this study, but only if the physician completes the case by following it to its conclusion. Unusual cases are valuable in that the registry offers an opportunity to collect data on a sufficient number for adequate study. Cases are not acceptable without at least a microscopic slide showing the pathologic condition, and blocks, either paraffin or pieces of tissue, are desired when they can be furnished. Complete data, as is indicated on the form, including the diagnosis of the local pathologist, should be furnished when possible. The registry will not act as a diagnostic laboratory, as reports will be rendered only after the cases have been carefully studied. Committees appointed by the association will study the cases and render reports at the meetings of the association.

While the registry is concerned only with tumors of the bladder and more particularly with the epithelial tumors of that organ, the Army Medical Museum also maintains the registry of tumors of the lymphatic system, under the auspices of the American Association of Pathologists and Bacteriologists.

Since the foundation of the Army Medical Museum in 1862, the institution has always been glad to receive rare and unusual specimens, particularly tumors, from any physician. The material is acknowledged to the donor and recorded in his name. Material is carefully studied, and a report and a slide are furnished when requested by the donor. The object of this work is to accumulate at the Army Medical Museum as many examples of tumors and rare conditions as possible, so that there may be a large collection for use in just such studies as has been inaugurated for bladder tumors by the American Urological Association and for tumors of the lymphatic system by the American Association of Pathologists and Bacteriologists. The curator is Major George R. Callender, Medical Corps, United States Army.

Funds for Cancer Research.—John D. Rockefeller, Jr., has given \$60,000 a year for five years to the Memorial Hospital in New York for cancer research. According to reports, the money is to be used for research on the problem of causation of cancer, for the training of specialists in the early diagnosis and

treatment of this disease, and for improving the nursing service in the hospital. The Memorial Hospital also has received \$25,000 from Lucius N. Littauer, for special research in chemotherapy over a period of five years.

Massachusetts Medico-Legal Society.—This society observed its fiftieth anniversary on October 5. It was organized when Massachusetts established its present system of medical examiners in 1877, and has been, and is, an important factor in maintaining a superior medicolegal service in that state. The society publishes a journal, which is unique, so far as this country is concerned, in representing sincere efforts to advance medicolegal practice and research.

DOCTORATES IN MEDICAL SCIENCES CONFERRED BY AMERICAN UNIVERSITIES 1926-1927 *

Callie Hull and Clarence J. West, Research Information Service,
National Research Council, Washington, D. C.

The following list of doctorates in Anatomy, Bacteriology, Pathology, Physiology, Physiologic Chemistry and Public Health granted during the academic year 1926-1927, has been compiled from information supplied through the courtesy of the various American universities granting the doctor's degree. Similar lists covering the years 1922-1925 and 1925-1926 were published in the ARCHIVES 1:259-262 (Feb.) 1926, and 3:274-276 (Feb.) 1927. It is offered again as a suggestive guide to the research work which is being carried on at different universities, and to the persons interested in special fields of investigation.

ANATOMY

- Brown: Helen Tucker Albro, "A Cytological Study of the Oenocytes."
Chicago: I Chuan Wen, "The Anatomy of Human Embryos with 17 to 23 Pairs of Somites."
Cornell: Lawrence Onis Morgan, "A Study of Secondary Degenerations Following Lesions of the Corpus Striatum in Man and Symptoms and Acute Degenerations Following Experimental Lesions in the Corpus Striatum of Cats."
Harvard: Barry Joseph Anson, "The Comparative Anatomy of the Lips and Labial Villi."
Kansas: Joseph Goering, "An Experimental Analysis of the Motor Cell Columns in the Cervical Enlargement of the Spinal Cord in the Albino Rat." Engelbrekt August Swenson, "The Development of Movement of the Albino Rat Before Birth."
Michigan: Elisha Stephens Gurdjian, "Studies on the Rat's Brain. Diencephalon."
Minnesota: Winifred Henry Buermann, "Clinical and Pathological Study of Carcinomatous Gastric Ulcer with Special Reference to the Grading of Malignancy." Charles Hamilton Watkins, "A Quantitative Study of the Growth of the Arterial System of the Human Fetus with Respect to Body Length, Body Weight, Heart Weight and Age."
Northwestern: Arthur Newton Ferguson, "Studies on Regeneration in the Gastric mucosa."
Howard Butters Kellogg, "Studies on the Fetal Circulation of Mammals."
Stanford: Sophie de Aberle, "Hereditary Anaemia in Mice."
Washington University, St. Louis: Joseph Clarence Hensey, "Some Observations on the Innervation of the Skeletal Muscles of the Cat."

BACTERIOLOGY

- Chicago: Gail Monroe Dack, "Studies on Clostridium Botulinum."
Cincinnati: Bernice Elaine Eddy, "Search for a Pneumococcal Agent During Crisis in Pneumonia."
Columbia: Arnold Henry Eggerth, "The Bactericidal Action of Acridine Dyes and the Adjuvant Effect of Serum." Elizabeth Lee Hazen, "General and Local Immunity to Ricin."
Cornell: Harry Benjamin Alger, "The Reaction of Bacterium Coli to Hydroxyl Ions in Unbuffered Solutions." Charles Franklin Poe, "A Study of the Media for the Production of Bacterial Fluorescence."
Iowa State College: James Milton Fife, "Studies in Nitrogen Fixation." Lincoln Spencer Hyde, "A Study of Some of the Lactobacilli."

* Information regarding the doctorates granted in all the sciences will appear in a forthcoming reprint of the National Research Council.

Johns Hopkins: Bettylee Hampil, "A Study of the Bactericidal Properties of the Alkyl and Acyl Derivatives of Resorcinol." Laban Wingert Leiter, "A Study of the Availability of the Eijkman Fermentation Test at 46 C. as an Aid in the Detection of Fecal Contamination of Water."

Massachusetts Institute of Technology: Kisaku Morikawa, "A New Fermentation Yielding Butyl and Isopropyl Alcohols."

Missouri: Anna Dean Dulaney, "The Convergence of Bacterial Types in the Colon Group as Shown by Serological Reactions." Charles Hughes Philpott, "Growth of Paramecia in Pure Cultures of Pathogenic Bacteria." Esther Wagner Stearn, "The Mutation of Characters of Bacteria as Defined by the Action of Gentian Violet in Its Staining and Bacteriostatic Effect."

Pennsylvania: Alice Tweed Marston, "Experiments on the Possible Infectious Nature of Diabetes Mellitus."

Rutgers: Rene Jules Dubos, "Concerning the Nature of the Flora Active in the Decomposition of Cellulose in the Soil, with Special Regard to the Activity of Bacteria in this Process."

Wisconsin: Edith Haynes, "A Study of Certain Hemolytic Streptococci of the Beta-Type in Certified Milk." Harry Gordon Harding, "The Occurrence and Significance of Thermophilic Bacteria in Milk." Harold Ray Thornton, "The Methylene-Blue Reduction Test."

Yale: Lawrence Henry James, "Heat Production by Microorganisms in Organic Materials."

PATHOLOGY

Chicago: Moses Abraham Jacobson, "Studies on the Epidemiology of Lobar Pneumonia."

Johns Hopkins: Clay G. Huff, "Studies on the Infectivity of Plasmodia of Birds for Mosquitoes, with Special Reference to the Problem of Immunity in the Mosquito."

Yale: William Franklin Wenner, "The Prevention of Parathyroid Tetany by Oral Administration of Magnesium Lactate and of Ammonium Chloride."

PHYSIOLOGIC CHEMISTRY

California: Anthony Joseph Salle, "The Metabolism of *Leishmania Tropica*."

Chicago: Grant Melvin Kloster, "Studies of the Effect of Varying Hydrogen Ion Concentration upon the Activation, Destruction, and Rate of Action of Proteolytic Enzymes in Gastric Mucous Membranes." Marguerite Genevieve Mallon, "Metabolism Experiment on the Adult Albino Rat Fed Once a Day; Observations on Calcium Metabolism." Clemmy Olin Miller, "The Asymmetry of Certain Hypnotics and Its Relationship to Physiological Behavior." Casper Irving Nelson, "The Intracellular Proteins of Bacteria: I. Globulins. II. The Globulins as Indicators of Interspecies Relationship." Alice Caroline Willard, "A Comparison of Evaporated with Pasturized Milk as a Source of Calcium, Phosphorus, and Nitrogen."

Cincinnati: Byron Curtis Brunstetter, "A Comparison of the Blood-Coagulation Mechanism with the Immune Hemolytic Mechanism." Emmett Bryan Carmichael, "Ricin, Its Nature and Action."

Columbia University: Mildred Adams, "A Quantitative Comparison of the Influence of Neutral Salts on the Activity of Pancreatic Amylase and Some of the Factors Involved." Olga Helen Marie Gloy, "Vitamin B Determination and Requirement with Special Reference to Protein Intake." David Mathews Grael, "The Hydrogen Ion Concentration of the Intestinal Contents under Various Conditions, with Special Reference to Rickets." Margaret Constance Hessler, "Experiments upon the Quantitative Differentiation of Vitamins A and D." Alma Elizabeth Hiller, "The Effect of Histamine on Protein Catabolism and on Acid-Base Balance." Edward H. Miller, "Influence of Hydrogen Ion Activity upon the Stability of Vitamin A." Winifred J. Wood, "Studies in the Velocity of Inactivation of Malt Amylase." Cornell: Isaac Neuwirth, "The Problem of Sugar in Normal Urine." Randall Whitaker, "A Study of Rennet Coagulation Using the Hydrogen and Sodium Electrodes for Determining Changes in Ion Concentration."

Harvard: Erik Harry Lundin, "Intermediary Carbohydrate Metabolism. On the Determination of Sugar in Biological Fluids. Some Factors Influencing the Capacity to Perform Muscular Work." Harry Henry Powers, "A Study of the Organic Phosphorus Compounds of Muscle."

Iowa: Elizabeth Julia Magers, "A Study of the Fifty Gram Glucose Tolerance Test with Reference to Sugar and Mineral Changes in Blood and Urine."

Iowa State College: Buford H. Butcher, "Study of the Metabolism of *Bacterium Coscoroba* on Gluconic Acid." Leo Martin Christensen, "The Fixation of Atmospheric Nitrogen by Yeast." Harold William Coles, "Laboratory Synthesis and the Digestion by Micro-Organisms of Certain Modified Sugars."

Johns Hopkins: Howard Wilmot Estill, "Chemical Studies Directed Toward the Isolation of the Fat-Soluble Vitamins A, D, and E." Marinus Cornelis Kik, "The Nutritive Value of Haddock and Herring (*Clupea harengus*)."

Michigan: Margaret Newell Woodwell Johnston, "A Comparative Study of the Rate of Metabolism of Certain Amino Acids." George Truman Lewis, "The Utilization of Some Organic Derivatives Containing Sulfur and of Elementary Sulfur by the Organism of the White Rat." Olive May Searle, "Metabolism in Psychoses. Fasting Blood Sugar and Glucose Tolerance."

Minnesota: Raymond Leslie Gregory, "A Study of the Quantitative Determination of Bile Salts."

Missouri: Hannah Stillman Bradfield, "Relation of Surface Area to Metabolism."

Ohio State: Charles Henry Hunt, "A Study of the Influence of Fertilizers on the Vitamin B Content of Wheat."

St. Louis University: Charles Neal Jordan, "A Micro-Chemical Study of an Ovarium Hormone." James Owen Ralls, "Preparation and Standardization of Active Follicular Hormone Extracts and Some Properties of the Hormone; Preliminary Report on the Effect of the Follicular Hormone on Basal Metabolism."

Tulane: Arthur Ordway Kastler, "Studies in Phosphate Metabolism."

Washington, Seattle: Roger Williams Truesdail, "The Vitamin A Content of Pacific Coast Salmon Body Oils."

Wisconsin: Roy Herman Baechler, "A Relationship Between the Chemical Formula and the Toxicity Toward Fomes Annosus of Certain Benzene Derivatives." Rolla Williams Titus, "The Nature of the Protein Surrounding the Fat Globule in Milk."

Yale: Verz Rogers Goddard, "Hemagglutinins of Plant Origin." Harvey Henry Harkins, "The Examination of Yeast Nucleic Acid for Methyl-Cytosine." Wilbie Scott Hinegardner, "A Study of Chaulmoogric Acid with the Object of Ascertaining the Cause of Its Therapeutic Effect."

PHYSIOLOGY

Brown: Kenneth Stillman Rice, "Studies of the Permeability of Artificial Membranes."

Bryn Mawr: Mary Summerfield Gardiner, "Oogenesis in *Limulus Polyphemus* with Especial Reference to the Behaviour of the Nucleolus."

California: Hazel Elizabeth Field, "Effects of Tobacco Smoke on the Activity of the Albino Rat." Lorenzo Phelps Laticier, "Physiological Changes Occurring in Pear Fruits During Growth and Ripening as Determined by Electrical Conductivity."

Chicago: Orpheus William Barlow, "A Comparison of the Pancreatic Secretagogue Efficiency of Various Standard Secretions, Sodium Nitrite, Peptone and Pilocarpine." Walter Lincoln Palmer, "The Mechanism of Pain in Gastric and Duodenal Ulcers." Erma Anita Smith, "Studies in Deficiency Disease." Wilbur Rudolph Tweedy, "Studies on the Plasma Calcium Raising Principles of Bovine Parathyroid Glands." George Earle Wakerlin, "The Motor Activity of the Gallbladder."

Cincinnati: Oliver Gatch Chance, "The Pharmacological Action of Tin in Organic Combination."

Cornell: Robert Claude Bradley, "The Loss of Weight in Eggs During Incubation and the Factors Affecting It."

Harvard: Philip Bard, "Diencephalic Control of the Sympathetic Nervous System."

Illinois: Walter John Richard Camp, "The Effect of Drugs on Number of Circulating White Blood Cells."

Johns Hopkins: Mary Hardy, "The Effect of Measured Amounts of Ultra-Violet Radiation on the Blood Count of Normal Rabbits." Annie Martha O'Donnell, "A Study of the Action of Ultra-Violet Light on Melanophores." Ethelberta Norris Rask, "The Photo-Dynamic Action of Hematoporphyrin." Charles Swingle, "A Physiological Study of Rooting and Callusing."

Massachusetts Institute of Technology: Bernard Emerson Proctor, "The Study of Residual Nitrogen as Shown by the Nitrogen Partition of the Renal Excretion."

Minnesota: Milo M. Loucks, "The Coagulation of Blood with Special Reference to Calcium, Thrombin and Prothrombin." Simon Marcovitch, "Studies on Toxicity of Fluorine Compounds." Arthur G. Mulder, "The Physiologic Chemistry of Fluorine."

Northwestern: James Irving Farrell, "Contributions to the Physiology of Gastric Secretion."

Ohio State: Rollin Ray Durant, "Studies in Blood Pressure." Edwin Poe Durrant, "Endocrine Studies on the White Rat."

Pennsylvania: Charlotte Haywood, "Carbon-Dioxide as a Narcotic Agent." Eugene Markley Landis, "Micro-Injection Studies of Capillary Permeability." Cecilia Riegel, "Lactic Acid Formation and Utilization in the Body."

Washington University, St. Louis: Francis Otto Schmitt, "The Conduction of the Impulse Through Cold Blooded Heart Muscle Locally Altered."

Wisconsin: Conrad Arnold Elvehjem, "Iron in Nutrition—Factors Affecting Hemoglobin Formation in the Animal Body." Frederick Earl Emery, "The Metabolism of Amino-Acids by *Paramecia Caudatum*." Forrest Draper McCrea, "Heart Studies: The Effect of Exercise on the Heart Size. The Action of Morphine in Slowing the Pulse." John Allen Wilson, "Some Mechanical Factors Influencing Cardiac Function."

Yale: Milton Irwin Rose, "The Respiratory Quotient of Exercising Muscle." Charles Joseph Stucky, "Some Physiological Effects of Diets Deficient in Vitamin B."

PUBLIC HEALTH

Massachusetts Institute of Technology: James Alner Tobey, "The National Government and Public Health."

Yale: Cora Emeline Gray, "Tuberculosis Mortality in the Original Registration States." Robert Jordan, "The Morbidity and Mortality of Anthracite Coal Miners." Philip Skinner Platt, "The Validity of the Appraisal Form as a Measure of Administrative Health Practice."

Abstracts from Current Literature

Pathologic Physiology

FACTORS OF A GROWTH REGULATORY NATURE IN TISSUE CELLS. A. FISCHER, Am. J. M. Sc. **173**:562, 1927.

Tissue cells are unable to divide and regenerate to form a cell colony in vitro, unless they are in protoplasmic interconnection with other cells of the same kind. Dying cultures of fibroblasts may be rejuvenated by the addition of new cultures of fibroblasts or by the addition of leukocytes. The latter form "provisional" anastomoses with the fibroblasts. Both additions apparently supply some necessary growth-regulatory substance of "desmone" not present in the culture medium, which circulates only in the living protoplasm, passing from cell to cell through fine anastomoses. The growth of pure epithelium is not promoted by the addition of fibroblastic tissue, nor is it possible to establish a physiologic unit of two pieces of pulsating heart tissue (adjustment of the pulsations to a common rhythm) after interposition of a layer of fibroblasts or when the two pieces of tissue are not of a common species origin. The regulating action of the desmones appears to be specific and may explain the failure of grafted cells to grow when they are not homologous with the cells of the host. Cells from malignant tumors appear to be able to synthesize the principles necessary for growth independently of association with other cells.

ARTHUR LOCKE.

KIDNEY FUNCTION IN ADRENAL INSUFFICIENCY [IN THE CAT]. F. A. HARTMAN; G. G. MACARTHUR; F. D. GUNN; W. E. HARTMAN, and J. J. MACDONALD, Am. J. Physiol. **81**:244, 1927.

Changes in the blood have been followed in suprarenalectomized cats, some of which survived more than thirty-five days. There was an increase in the blood solids. The blood sugar became less in the later stages, reaching as low as 50 per cent of the normal at death in some animals. The calcium, creatinine and uric acid in the blood were slightly above normal. The acid-soluble phosphates of the blood were considerably higher than normal in the later stages. The blood urea increased, and this increase ran parallel to some extent with the loss of appetite and other symptoms. The ingestion of liver caused a marked increase in blood urea and an exacerbation of the symptoms. The anatomic changes which appeared rather constantly were: purplish discoloration of the gums, hemorrhages in the thymus, general hyperemia of the internal organs and an accumulation of large quantities of lipoid substances in the tubuli contorti.

AUTHORS' SUMMARY.

HYPERMOBILITY OF JOINTS AS A SEX LINKED HEREDITARY CHARACTERISTIC. J. ALBERT KEY, J. A. M. A. **88**:1710 (May 28) 1927.

General hypermobility of the joints may occur as a congenital abnormality. The condition appeared spontaneously in a father and was transmitted to all the sons but not to any of the daughters. In the second generation of this family, the condition was associated with congenital deformities of the feet.

AUTHOR'S SUMMARY.

HYPOTENSION (SIX CASES IN ONE FAMILY). JOHN D. GARVIN, J. A. M. A. **88**: 1875 (June 11) 1927.

Six patients with low blood pressure in one family are in excellent health and are active and vigorous; most of them are robust and hypersthenic and one is obese. Incidental hypotension is of little if any clinicopathologic significance, except as a possible indicator of long life. Incidental hypotension has been misunderstood, in the past, and misinterpreted; a more rational attitude toward it, both on the part of the medical profession and, through it, by the laity, should be adopted. Hypotension, like hypertension, may be hereditary.

AUTHOR'S SUMMARY.

DIABETES AND PREGNANCY. C. G. LAMBIE, J. Obst. & Gynec. Brit. Emp. **33**:563, 1926.

This is a complete review and summary of the glycosurias and acetonurias occurring during pregnancy, and the effect of diabetes mellitus on fertility, on the menstrual cycle and on pregnancy.

A. J. KOBAK.

A CONTRIBUTION TO THE PATHOLOGY AND CAUSATION OF DYSMENORRHEA. B. WHITEHOUSE, J. Obst. & Gynec. Brit. Emp. **33**:607, 1926.

Unconceptional dysmenorrhea, as Whitehouse terms that type associated with expulsion of tissues from the uterine cavity in flakes, plaques or casts is considered a clinical and pathologic entity. The severity of the pain is dependent on the degrees of denudation of the endometrium and on the size of the fragments expelled. Anatomic defects and pathologic changes in the uterus are but secondary factors in producing pain. In most of the cases studied in which the patients had dysmenorrhea, the uterus was normal. The tissues cast off usually consisted of hyperplastic endometrium resembling decidua. Whitehouse considers the menstrual cycle a diphasic phenomenon, the positive phase lasting from the formation of the corpus luteum to its disintegration, and the negative phase from the latter to the time of the discharge of the ovum from the graafian follicle. Excessive lutein activity or high vitality of the ovum during the positive phase may cause a degree of menstrual hyperplasia that can be shed off only in casts or flakes at the end of each menstrual cycle, with the concomitant discomfort of dysmenorrhea.

A. J. KOBAK.

OBSERVATIONS ON THE CIRCULATION RATE IN MAN BY THE ETHYL IODIDE METHOD. H. W. DAVIES and A. R. GILCHRIST, Quart. J. Med. **20**:245, 1927.

The authors introduce a modification of the apparatus used by Henderson and Haggard by substituting nonflexible metal tubing in place of the rubber tubing. Rubber absorbs ethyl iodide and gives too high readings. All rubber parts were reduced to a minimum, and the metal tubing was coated on the inside with red lead. The valves were replaced by Loven's valves, which reduce the amount of condensed moisture. The ethyl iodide in the spirometer was kept well mixed by a fan. The authors describe their technic. One hundred and eighteen determinations were made in eighteen subjects. They claim that repeated observations at short intervals on the same day on a single person are likely to be fallacious, probably because of the depressant action of unhydrolyzed ethyl iodide in the blood. In this series there appeared to be no relation between the rate of circulation and body surface. The rate was compared with the basal metabolic rate, and the effect of muscular exertion was studied. The basal metabolic rate tends to return to normal quicker than the circulation rate. The conditions under which the rate is taken must be carefully controlled, as metabolism, temperature, posture, excitement and other factors affect the results.

N. ENZER.

INFLUENCE OF SELENIUM COMPOUNDS ON THE BLOOD VESSELS. A. H. ROFFO and R. LOPEZ RAMIREZ, *Bol. Inst. Med. Exper.* **4**:110, 1927.

Intravenous injections of rubidium selenate (Rb_2SeO_4) and potassium selenate (K_2SeO_4) in 1 per cent solutions in the toad or the dog produces vasoconstriction in which the nervous system plays no part. Rubidium selenate is more active than potassium selenate.

THE SIGNIFICANCE OF THE MEDIAN LOBE OF THE CEREBELLUM IN THE REGULATION OF BLOOD SUGAR. T. SHINOSAKI, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **106**:483, 1926.

The author describes a case of congenital diabetes with an old severe encephalitis in the cerebellar uvula. Using this as a basis, he found that by cutting this area superficially only in dogs, he was able to produce hyperglycemia up to 275 mg. for a period as long as four days. He shows that the cerebellar uvula receives the caudal fibers from the spinocerebellar tract and gives rise to fibers which end in the hypothalamus by way of the superior cerebellar peduncle. He concludes that the afferent arc of the reflex concerned with the regulation of blood sugar is contained in the cerebellar uvula.

ROY GRINKER.

THE ETIOLOGY OF THE VASONEUROSES. M. LAPINSKY, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **106**:613, 1926.

After an exhaustive review of the literature and the citation of many illustrative cases, the author concludes: 1. Vascular spasms or dilatations in distant parts of the body signify a visceral disease located so that the centripetal fibers enter the vasomotor centers at the same segment as those fibers innervating the part of the body affected. 2. Vasospasms and vasodilation may both be associated with peripheral pain. 3. A disease of the liver or gallbladder or other internal organ may result in spasm, dilatation or pain in the peripheral vessels. 4. Vasomotor neuroses, such as acrocyanosis, acroparesthesia and Raynaud's disease, may result from visceral disease. 5. This long continued vasospasm or dilatation due to visceral disease may result in an organic disease of the walls of peripheral vessels due to an insufficient supply of blood to the vasa vasorum.

ROY GRINKER.

Pathologic Anatomy

PRIMARY INFECTION IN TUBERCULOSIS. E. G. STOLOFF, *Am. J. Dis. Child.* **33**:363, 1927.

In 6,329 roentgenologic examinations of chests showing tuberculous infection only 9.5 per cent revealed the primary focus, whereas postmortem examinations by Ghon revealed the primary focus of infection in 95 per cent of cases. The pathologic change and pathogenesis of primary pulmonary infection, adjacent pleuritic involvement and associated disease of the regional lymph glands are described and the discrepancies between the fluoroscopic and anatomic observations are explained on the basis of physical factors.

RUTH TAYLOR.

ESSENTIAL HEMATURIA AND ITS POSSIBLE RELATIONSHIP TO PURPURA HEMORRHAGICA. H. MILTON CONNER and HERMON C. BUMPUS, JR., *Am. J. M. Sc.* **173**:176, 1927.

Of twenty-two cases of unquestioned essential hematuria, the average platelet count was less than 150,000 in twelve cases, and of eleven cases of probable essential hematuria, the average platelet count was less than 150,000 in ten cases.

The platelet average of 141,000 and 131,000 respectively, in the two groups is only a little in excess of half the normal. The decreased number of platelets, together with the positive tourniquet test in a rather high percentage, suggests that it is possible that a deficiency in platelets may be responsible for the bleeding, as in purpura hemorrhagica.

The response to local applications of silver nitrate in many cases suggests a local predisposing cause in the kidney, while the response to the use of the serum of the horse or man and to injections of autogenous whole blood is suggestive of its origin in deficiency of coagulation or of blood platelets. It is likely that both may exist in many cases.

In seven healthy men the average platelet count was 198,000; in twelve cases of definite purpura hemorrhagica the average platelet count was 85,000, while in cases in which there had been recent hemorrhage from the urinary tract, not accompanied by any evidence of purpura hemorrhagica, the average platelet count was 231,000.

H. M. CONNER.

SICKLE CELL ANEMIA: REPORT OF A CASE WITH AUTOPSY. GORDON E. HEIN, R. L. MCCALLA and W. G. THORNE, *Am. J. M. Sc.* **173**:763, 1927.

The authors report a typical case of sickle cell anemia in a male negro, aged 20. Death resulted from duodenal ulcer and peritonitis. The spleen was shrivelled and small and contained several small, hemorrhagic infarcts; the marrow was deep red and contained numerous normoblasts.

SYNCYTIAL ENDOMETRITIS AND SYNCYTIIUM. M. ROSENZWEIG, *Am. J. Obst. & Gynec.* **13**:563, 1927.

Rosenzweig presents two cases: one, a syncytial endometritis characterized by isolated invasions of syncytial cells in the endometrium, accompanied by a leukocytic reaction, and the other, a syncytioma characterized by the occurrence of syncytial cells in masses and sheets in the endometrium. Both are considered transitional lesions of the chorioma group, being essentially benign and not showing any Langhans cells or villi. A review of the literature shows that these lesions are not generally recognized and that malignant chorionic growths are less frequent than was previously supposed.

A. J. KODAK.

BONE MARROW IN PERNICIOUS ANEMIA. FRANCIS W. PEABODY, *Am. J. Path.* **3**:179, 1927.

The study of marrow obtained by biopsy of different stages showed that myeloid hyperplasia is most marked during relapse and that the marrow tends to return to normal during remission. The anemia of the relapse is attributed to functional ineffectiveness of the marrow, because megaloblasts fail to develop toward mature erythrocytes. It is suggested that the good results from feeding liver in pernicious anemia may be due to some factor in the liver that promotes the formation of mature red cells.

RETICULUM IN REPAIRS OF TUBERCULOUS LESION WITH AND WITHOUT CASEATION. WM. SNOW MILLER, *Am. J. Path.* **3**:217, 1927.

As the repair in a tubercle progresses, the fibers of reticulum at its periphery increase in thickness and gradually become collagenous. In the absence of caseation the entire tubercle may become converted into collagenous tissue from such a change in the reticulum. The transition from reticulum to collagenous fibers can be followed in sections impregnated by the silver method.

TUBERCULOSIS OF TONGUE. WM. H. FELDMAN, *Am. J. Path.* **3**:241, 1927.

A case of tuberculosis of the tongue is described, and the available literature since 1916 is reviewed.

HISTOGENESIS OF URINARY CASTS. HENRY JACKSON, JR., *Am. J. Path.* **3**:285, 1927.

In chronic nephritis, certain casts may form by coalescence of granules in the circular reticulum formed by an abnormal budding of renal cells.

CHANGES IN THE KIDNEY IN ADRENAL INSUFFICIENCY IN THE CAT. F. A. HARTMAN, C. G. MACARTHUR, F. D. GUNN, W. E. HARTMAN and J. J. MACDONALD, *Am. J. Physiol.* **81**:244, 1927.

Thirty-five cats were examined from two to thirty-eight days after adrenalectomy. In addition to purplish discoloration of gums, hemorrhages in the thymus, hyperemia of internal organs there was a constant and striking increase in the lipid content of the renal cortex. Lipoid material was present in the tubular epithelium in large and small droplets. Staining for the most part orange or orange-red with sudan III, red or bluish red with Nile blue sulphate and, in smaller degree, black with osmic acid.

THE EFFECT ON THE JEJUNAL MUCOSA OF TRANSPLANTATION TO THE LESSER CURVATURE OF THE STOMACH. G. DE TAKATS and F. C. MANN, *Ann. Surg.* **85**:698, 1927.

Typical peptic ulcer occurred in three of twenty-five jejunal transplants. The transplant was made in the lesser curvature of the stomach. Great care was exercised to maintain an intact blood supply to the transplanted tissue. In transplants into other portions of the stomach, ulcers consistently failed to develop. The inference is that the chemical action of the gastric juice plus the important mechanical factor of position in the line of stress operate in the production of a chronic peptic ulcer.

N. ENZER.

SPLEENS FROM GAUCHER'S DISEASE AND LIPOID-HISTIOCYTOSIS. W. BLOOM and R. KERN, *Arch. Int. Med.* **39**:456, 1927.

The microchemical reactions of the material present in the large cells in lipoid-histiocytosis (Niemann's disease) indicate that this material is lipid in character and probably belongs to the phosphatide group. In Gaucher's disease the large cells do not give any of the lipid reactions in typical manner. They usually give the reaction for iron. Chemical analyses prove that the spleen in Niemann's disease contains less total nitrogen than in Gaucher's disease or under normal conditions, but a decidedly increased amount of phosphorus. The total ether and alcohol soluble extractives are also greatly increased in Niemann's disease. The stored material in lipoid-histiocytosis is chiefly phosphatides, probably lecithin and cholesterol. In Gaucher's disease, the material is chiefly kersin.

AUTHORS' SUMMARY (S. A. LEVINSON).

TORSION OF THE GALLBLADDER. A. M. SHIPLEY, *Arch. Surg.* **14**:968, 1927.

Torsion occurs only when the gallbladder is surrounded by peritoneum and attached to the liver by a mesentery. Twenty-one cases were found in the literature, nineteen of which were in women who had visceroptosis. The onset of the symptoms was sudden with severe pain and vomiting. At operation, serosanguinous fluid was found in the peritoneal cavity, and the wall of the gallbladder was thickened and hemorrhagic. The viscus was frequently distended and filled with blood. In seven cases, stones were present, not any of which were impacted. Perforation occurred in one instance. The direction of the volvulus was not constant. The author describes a case from his own experience.

N. ENZER.

FRACTURE OF THE SKULL—COMPLICATIONS AND CAUSES OF DEATH. B. M. VANCE, Arch. Surg. **14**:1023, 1927.

The necropsy observations in 512 cases of fracture of the skull are analyzed. Five of these were in children under 5 years of age four of whom died of cerebral concussion and one of subdural hemorrhage and laceration of the brain. Of the remaining 507 patients, death was due to cerebral concussion in 139, the majority dying in the first hour and all within ten hours after the trauma. Fourteen of the patients died of exhaustion in from one to twenty days. Twenty-seven died of terminal bronchopneumonia, the onset of which was from two to nine days after the injury. Cerebral compression due to subdural hemorrhage was the cause of death in 132 cases, and laceration of the brain in twenty-four. Sixty-one cases of epidural hemorrhage resulted in death in from one to fourteen days. Forty-one instances of acute leptomeningitis occurred in fractures through the cranial sinuses and lasted for from several days to several weeks. Septic infection was the cause of death in seven cases, the portal of entrance being through compound fracture. Four patients died of operative interference and three of traumatic epilepsy in from six months to two years after the injury. Thirty died of other injuries received at the time, and twenty-five of other conditions. These statistics are amplified by descriptions of the lesions and fractures and the mechanism in operation. Sixty-one cases are analyzed from the clinical standpoint. Thirty-four patients presented indications for operation and eleven recovered; twenty-seven were treated without operation and recovered. The latter lacked the signs and severity of symptoms which led to operation in the other thirty-four. The symptomatology and pathology are fully discussed.

N. ENZER.

LOBAR ATELECTASIS IN CHRONIC PULMONARY SUPPURATION. E. D. CHURCHILL and G. W. HOLMES, Arch. Surg. **14**:1093, 1927.

In atelectasis of the lower lobe a characteristic roentgenogram is produced. It appears as a triangular opacity which obliterates the cardiophrenic angle on the right but is largely obscured by the shadow of the heart on the left. Six cases of chronic suppuration are presented, all of them associated with atelectasis of the involved lobe. In four of these the onset of symptoms followed a surgical procedure, severe trauma or postdiphtheritic paralysis. One patient gave a history of a severe pulmonary infection, and the sixth a history suggestive of the presence of a foreign body. This suggests that the condition of atelectasis was primary and that it was followed by stagnation of bronchial secretion and pulmonary suppuration.

N. ENZER.

THE PATHOLOGICAL FINDINGS IN FOUR AUTOPSIED CASES OF ACROMEGALY WITH A DISCUSSION OF THEIR SIGNIFICANCE. HARVEY CUSHING and LEO M. DAVIDOFF, Monographs of the Rockefeller Institute for Medical Research, 22, April 23, 1927.

Four cases of acromegaly of differing clinical types are described, illustrating the kaleidoscopic pathologic anatomy of the disease. In one patient, a man of huge frame, the general splanchnomegaly and widespread changes in the endocrine series quite overshadowed the small hypophysial lesion. In another, an acromegalic giant, the neighboring symptoms of the tumor dominated the picture. The two other patients were small. In one of them an enormous intracranial adenoma, unsuspected during life, was masked by cardiovascular and diabetic symptoms, and at autopsy adenomas were found in many of the ductless glands. In the other, on the contrary, a woman who died from diabetic coma, the postmortem observations were relatively insignificant, and the hypophysial tumor was small.

Of the two patients who had the smallest hypophysial lesions, one was small and the other was gigantic. Of the two patients who had the largest hypophysial adenomas, one was small and the other was an acromegalic giant. Of the two acromegalic giants, one had extreme cardiovascular changes, the other but slight changes; the same was true of the two small persons.

The only constant pathologic observations in all cases were: (1) the commonly recognized overgrowth of the mesodermal tissue; (2) the less commonly emphasized and disproportionate splanchnomegaly, which chiefly affected the liver and kidneys; (3) the more or less general polyglandular anomalies accompanied by a tendency to adenomatoses, and (4) a central hyperplasia (two cases) or an adenoma of the hypophysis (two cases), the cells composing the lesion in all four instances containing demonstrable acidophilic granules.

Though in the early studies of acromegaly chief stress was laid on the hypertrophic changes in the periphery, chiefly the acral tissues, on the enlargement of parts of the central nervous system and, finally, on the hypophysial tumor, the general splanchnomegaly, though appreciated, was lost sight of, and the condition of the other ductless glands was only casually mentioned. Of late years, these latter aspects of the malady have come more into the foreground.

Many theories have been advanced in explanation of acromegaly, and these were presented by one of us in an earlier paper in the series. One author ascribes the enlargement of the pituitary to a secondary effect of the disease; another considered the disorder to be polyglandular in nature, the hypophysis playing only a part, which happens to be striking merely because of the accident of its anatomic location; another attributes the malady solely to the anterior lobe and to certain of its cells which become functionally modified so as to produce a profound change in the general metabolism of the body.

Even today, any one of these theories on a purely histopathologic basis might be sustained by telling arguments, but the unescapable fact remains that all cases of acromegaly show an acidophilic adenoma of the hypophysis. Moreover, extracts of the part of the gland from which these adenomas arise alone are capable of producing in an experimental animal not only overgrowth of the mesoblastic tissues but splanchnomegaly as well, together with changes in the ductless glands comparable to that seen in acromegaly and gigantism.

Acromegaly, then, is a chronic disease of adult life, outwardly characterized by the acral changes first emphasized by Marie. The pituitary body, though not invariably enlarged, is usually, and sometimes enormously, increased in size by a hyperplastic or adenomatous process composed of acidophilic cells. These granular cells elaborate or at least hold a hormone which, when injected into certain animals, provokes overgrowth (gigantism), and which are almost certainly the cause of acromegaly and gigantism in man.

As an accompaniment of the disease, a general splanchnomegaly of the viscera usually occurs which is disproportionate to the general enlargement of the body. In addition, notable glandular changes often associated with adenomas occur in the other endocrine organs, giving to the malady its unusual polyglandular aspects. Almost always an increase in the suprarenal cortex is noted; usually an enlarged or persistent thymus; in about a third of the cases a colloid goiter; often enlargement of the parathyroids; often a functional derangement of the pancreatic islets, and invariably changes indicative of atrophy or dysfunction of the gonads.

It is safe to say that a derangement of the pituitary anterior lobe affects the body as a whole far more seriously than a primary derangement of any other member of the endocrine series. Figuratively speaking, it may be said to represent the keystone of the endocrine arch.

AUTHORS' SUMMARY.

CONGENITAL ABSENCE OF TIBIA. E. L. EVANS and N. R. SMITH, Arch. Dis. Child. **1**:194, 1926.

A complete study of the anomaly of congenital absence of the tibia, with descriptions of three cases, is presented. The cause is thought to be defective development of the mesoblast under an influence at present unknown, but not traumatic, mechanical, vascular or atavistic.

A CASE OF AN INTESTINAL SAC AT THE SITE OF MECKEL'S DIVERTICULUM. F. J. JAUCH, Brit. J. Surg. **14**:576, 1927.

A localized saclike dilatation of the ileum, 63 cm. from the ileocecal valve, containing an afferent and an efferent loop of ileum, was thought to be a dilated and hypertrophied Meckel's diverticulum.

BENSON BLOOM.

INTRATHORACIC NEW GROWTHS: AN ACCOUNT OF SEVEN OPERABLE CASES. A. T. EDWARDS, Brit. J. Surg. **14**:607, 1927.

Three cases of teratoma, one of chondrosarcoma, one of lipofibrosarcoma, one of endothelioma and one of a cyst in the pleural cavity, all of which were of undetermined origin, are reported. The tumors were excised successfully in six cases; in one case, in which lobectomy was performed for an endothelioma, death was due to postoperative intrapleural hemorrhage. Pneumothorax, thoracoscopy, injection of iodized oil and examination of the esophagus after a bismuth meal were used to localize the tumors.

BENSON BLOOM.

SOLITARY CYSTS OF THE KIDNEY. A. FULLERTON, Brit. J. Surg. **14**:629, 1927.

Solitary cysts of the kidney, a relative rare condition, is discussed and another case, of solitary serous cyst, is added to the ninety-eight previously reported in the literature.

BENSON BLOOM.

SOME OBSERVATIONS ON THE BONE CHANGES IN RENAL RICKETS. E. P. BROCKMAN, Brit. J. Surg. **14**:634, 1927.

Three cases of renal rickets in children are reported, in one of which, a case of polycystic kidney, necropsy was made. In this condition, as compared with ordinary rickets, the shaft of the bone remains straight, the deformity being due to dislocation of the epiphysis; the marrow is replaced by fat; there is marked bone absorption with little bone formation; the arteries of the medulla are thickened, and the increase in the amount of fibrous tissue and in the number of capillaries is more extensive than in ordinary rickets. It is suggested that the changes in the bone result from a toxic condition, due to renal failure, affecting the delicate cells of the growth disk and the medulla.

BENSON BLOOM.

A CASE OF *B. WELCHII* CHOLECYSTITIS. E. P. GOULD and L. E. H. WHITBY, Brit. J. Surg. **14**:646, 1927.

Bacillus welchii was isolated from the bile and also from the crushed gall stones, the intact stones being sterile. The mucosa contained numerous areas of gangrene. Only two cases of infection of the gallbladder by *B. welchii* had previously been reported.

BENSON BLOOM.

A CASE OF ALBERS-SCHÖNBERG'S DISEASE. H. R. SEAR, Brit. J. Surg. **14**:657, 1927.

The features of Albers-Schönberg's disease are extreme density of all the bones, especially the ends of the diaphyses; marked anemia; enlargement of

the liver and spleen; pressure on the cranial nerves; hydrocephalus; interference with dentition, and necrosis of the jaw. A case is reported in a boy, aged 6 years. Necropsy was not performed.

BENSON BLOOM.

PYLORIC OBSTRUCTION IN AN INFANT FROM PRESSURE OF A DISTENDED GALL-BLADDER. H. H. GREENWOOD, *Brit. J. Surg.* **14**:663, 1927.

The cystic duct was represented by an impermeable fibrous cord. The gallbladder was enormously distended with clear watery fluid; the antrum, pressing on the second portion of the duodenum, produced the obstruction.

BENSON BLOOM.

A CASE OF PRIMARY CARCINOMA OF THE APPENDIX. G. WOOD-WALKER, *Brit. J. Surg.* **14**:665, 1927.

The case reported is evidently an example of carcinoid of the appendix.

BENSON BLOOM.

A CASE OF HYDATID DISEASE OF THE KIDNEY. E. T. WILLANS and M. J. STEWART, *Brit. J. Surg.* **14**:667, 1927.

The cysts were apparently dead, scolices or hooklets not being found, although fragments of laminated ectocyst were seen in the necrotic lining.

BENSON BLOOM.

ANEURYSM OF THE FEMORAL ARTERY IN A PATIENT WITH POTT'S DISEASE OF THE SPINE. E. P. BROCKMAN, *Brit. J. Surg.* **14**:669, 1927.

Tuberculosis of large arteries is rare. A case is reported in which all the coats of the femoral artery were involved in a tuberculous process. The aneurysm which formed ruptured spontaneously. It is thought that the involvement of the artery wall occurred by means of the vasa vasorum.

BENSON BLOOM.

FOREIGN BODIES IN THE ILEAL (MECKEL'S) DIVERTICULUM, WITH FORMATION OF A PEDUNCULATED CYST WHICH STRANGULATED A LOOP OF SMALL INTESTINE. H. MILLER, *Brit. J. Surg.* **14**:678, 1927.

The cyst, containing a mucus-like fluid and a number of foreign bodies (seeds, etc.), apparently resulted from closure of the diverticulum by growth of a plica circularis, producing a diaphragm lined on both sides by mucous membrane.

BENSON BLOOM.

ENDOMETRIAL TUMORS OF LAPAROTOMY SCARS. G. W. NICHOLSON, *J. Obst. & Gynec. Brit. Emp.* **33**:620, 1926.

Nicholson abstracted and reviewed the cases of endometrial tumors in laparotomy scars in the literature, including his case previously reported. Tumors in laparotomy scars were found at the average age of 36 years. They were associated with menstrual disturbances and were found from as early as a few weeks to twenty years postoperatively. Nicholson rejects the embryonic and displacement theories of their origin. He accepts the peritoneal theory, and, since the endometrium arises from cells of the celom, the peritoneal epithelium may again by suitable stimuli undergo metaplasia and produce endometrium. The endometrial tumors are regarded by the author as acquired accessory uteri.

A. J. KORAK.

STRIAE PATELLARES FOLLOWING TYPHOID FEVER. J. D. ROLLESTON, *Proc. Roy. Soc. Med.* **20**:9, 1927.

Transverse symmetrical purplish stripes, located $1\frac{1}{2}$ inches (3.7 cm.) above the upper border of each patella, from 1 to $1\frac{3}{4}$ inches (2.5 to 4.4 cm.) in length were observed in a patient convalescent from typhoid fever. The condition, known to occur in growing people after acute infectious disease, is thought to represent distention below the cutis leading to cleavage of the deeper layers of the skin.

RUTH TAYLOR.

PIGMENTED CELLS IN THE MAMMARY GLANDS OF CATS AND THEIR SIMILARITY TO THE INTERSTITIAL CELLS. P. GERARD, *Arch. internat. de méd. expér.* **3**:139, 1927.

Pigmented cells varying from five to twenty microns in diameter occur in the mammary glands of pregnant cats. Their occurrence is irregular and they are most frequent in animals carrying embryos from 80 to 117 mm. in size. They are present, chiefly, in the interacinous and interlobular connective tissue. They were found, however, in the epithelium of the acini and ducts and occasionally, also, in the lumen of the ducts. The characteristic feature of these cells is their content of granular material which Gerard by specific stains showed to be a combination of a lipoid and a protein with a pigment of the melanin group. He believes that these cells have a triple origin. The majority are probably evolved from clasmotocytes, i. e., the large, round, wandering cell of Maximow and the adventitial cell of Marchand. A few appear to be derived from lymphocytes and a smaller number from fibroblasts. He could not find any relation between these cells and the interstitial cells or mastocytes. Gerard believes that the pigment is the same as that found in the secreting epithelium and that it is taken up by these wandering cells only under abnormal conditions to compensate for the failure of the epithelial cells to absorb the constituents of this lipopigment from the blood.

N. ENZER.

EXPERIMENTAL XANTHOSIS OF THE EYE. W. ROHRSCHEIDER, *Arch. f. Ophth.* **118**:131, 1927.

Streptococci suspended in physiologic salt solution were injected into the anterior chamber of the left eye of rabbits, after removal of the aqueous humor. Yellow discoloration developed in the anterior part of the eyeball. Microscopic examination of sections of the eye revealed lipoid deposits, containing cholesterol esters. The fatty degeneration of the eyeball is not an infiltrative process, but the result of local intra-ocular processes. The lipoids were probably produced by fatty decomposition of infectious exudates. The microscopic and macroscopic features closely resembled the changes in the human eye known as xanthosis of the eyeball.

REACTION OF LUNG TO DUST INHALATION. F. GROSS, *Beitr. z. path. Anat. u. z. allg. Path.* **76**:374, 1927.

In order to study the reactive changes in the lymph nodes of the lung and hilum to inhaled tubercle bacilli and dust, Gross subjected rabbits to inhalation of such materials. In the case of tubercle bacilli, the animals received a single inhalation. The dust used consisted of fine wood charcoal and fine quartz, the animals being subjected daily for one to two hours to an atmosphere laden with these materials, and the daily treatment being continued from six to ten months. Some of the animals were killed immediately after the cessation of the period of inhalation, others were permitted to live from one to six months.

In another series, rabbits that had received a single inhalation of tubercle bacilli were subjected to dust inhalation for two months, and still another series that had been subjected to dust for nine months received a single inhalation of tubercle bacilli. The chief reaction was ascribed to the alveolar epithelium, which proliferates, desquamates and phagocytizes the inhaled material. The degree of epithelial reaction was least after carbon dust and greatest after tubercle bacilli. The same gradation applied to the mesenchymal reaction, which was absent in anthracosis, slight in silicosis and marked in tuberculosis. Anthracosis did not lead to induration of the bronchial lymph nodes. Dust inhalation, whether it preceded or followed the inhalation of tubercle bacilli, did not have any detectable effect on the tuberculous process.

O. T. SCHULTZ.

RELATIONSHIPS BETWEEN MONOCYTES AND HISTIOCYTES. M. MASUGI, Beitr. z. path. Anat. u. z. allg. Path. **76**:396, 1927.

In a study of the blood of the peripheral and visceral vessels of normal rabbits and of rabbits in which a monocytosis had been produced by the intravenous injection of various colloidal substances, Masugi employed the method of supravital staining with neutral red and janus green and the May-Gruenwald-Giemsa method for dry smears. On the basis of the supravital stain he believes that the monocytes represent a well characterized cell type which has nothing in common with either lymphocytes or leukocytes, and which is morphologically and functionally closely related to the histiocytes. He derives the phagocytizing, dye-storing histiocytes and the monocytes from the resting histiocytic elements scattered all over the body. These latter elements contain many mitochondria and but few or no neutral red vacuoles; the red vacuoles develop when the cells begin to function. Monocytes can develop in the animal organism, as well as *in vitro*, into histiocyte-like cells, but they cannot become lymphocytes or leukocytes. Histiocytes do not circulate in the blood except, perhaps, after the injection of certain poisons, or agonally. In incubated citrated blood of the rabbit, the monocytes becomes hypertrophied after a few hours and can be distinguished from histiocytes only with great difficulty. Masugi does not agree with Cunningham, Sabin and Doan that the neutral red rosette is of great value as a distinguishing characteristic of the monocyte.

WILLIAM BLOOM.

THE CAUSE OF DEATH IN THE NEW-BORN. H. HOOK, Beitr. z. path. Anat. u. z. allg. Path. **77**:456, 1927.

Hook shows that in addition to cerebral hemorrhage, infection, especially a confluent pneumonia following the aspiration of infected amniotic fluid, is an important factor in the death of new-born babies. This conclusion is based on the observations from numerous necropsies on new-born infants. His series of cranial hemorrhages is divided into those with definite evidence of trauma from birth, as qualified by injuries to the scalp, cephalhematoma and tears into the cerebellar tentorium; and those not due to external trauma, in which the foregoing qualifications are missing. The majority of his cases fall into the latter group. Hemorrhage in these cases is not considered the essential cause of death but a preagonal or agonal manifestation. The external mechanical stress of birth in a condition of circulatory stasis, or a toxic infectious factor, plays an important rôle in causing nontraumatic hemorrhage. In support of this view are two infants whose mothers died of gas poisoning and heart failure due to endocarditis before labor began; both infants had cranial hemorrhages. The presence and significance of fatty granules in and about the cells

of the glia are discussed at length. This process was minimal when vascular stasis was marked. The association of this condition with infections at distant foci was noted in fifteen cases, in eight of which cerebral hemorrhage did not occur. Fatty changes are conceded to be a sign of fatal trauma from birth, if etiologic factors other than hemorrhage can be ruled out, and if the localization is in a region of the brain that might undeniably cause death. Antenatal aspiration was noted in forty-three of fifty-four lungs examined. A focal confluent pneumonia followed, especially in cases associated with ruptured membranes over a long period, and when the mother was suffering from intrapartum fever. When the pulmonary reactions were slight, the cranial hemorrhage seemed to point definitely to the cause of death. Hook's work indicates that despite the cranial observations, the examination of other organs may be necessary to ascertain the cause of death.

A. J. KOBAK.

THYROIDS OF SWINE OF ENDEMIC GOITER REGIONS. E. CLERC, *Beitr. z. path. Anat. u. z. allg. Pathol.* **76**:494, 1927.

Clerc made a histologic study of the thyroids of swine of Bern Canton, Switzerland, which is in the human endemic goiter region. Such thyroids were compared with those of swine from Kiel, where endemic goiter does not occur. In the goiter region the thyroids of swine showed the same changes as the glands of human beings and of other species of animals in such regions, the changes consisting of diffuse hyperplasia with varying degrees of reversion to the colloid goiter state. The iodine content of the Bern thyroids was lower than that of the Kiel glands. Since animals from the same group sometimes showed variations in the degree of hyperplasia or reversion present, Clerc concludes that iodine deficiency alone does not explain the thyroid changes, although food and water do not seem to be etiologic factors.

O. T. SCHULTZ.

A CONTRIBUTION TO THE PATHOGENESIS OF MAMMARY CYSTS. HELENE HERZENBERG, *Centralbl. f. allg. Path. u. path. Anat.* **39**:229, 1927.

In a full term male infant dying soon after birth from compression of the lung by intestine herniated through a diaphragmatic defect, the following observations were made. Pea-sized, red masses in both breasts contained, microscopically, cystic enlarged apocrine sweat glands between numerous blood-forming islands and hypertrophied, irregularly formed breast gland acini and ducts. The cysts had a lining of high, pale eosinophilic, cylindrical epithelium, round, light, basal nuclei with one large and two small nucleoli, a fine, golden yellow granulation and occasional vacuoles in the distal part of the protoplasm. In the lumens were small droplets. The observation substantiates Krouncevich's theory of origin of mammary cysts from an "atavistic throwback," to apocrine sweat glands.

GEORGE RUKSTINAT.

THE EFFECTS OF VARIOUS TOXIC AND CHEMICAL STIMULI ON THE CIRCULATING LEUKOCYTES. R. A. HICKLING, *Folia haemat.* **33**:199, 1927.

Leukocytic variations differ both in degree and in kind in infective suppurations, in infective exudations and in noninfective suppurations. This statement applies both to man and to experimental animals. Evidence is adduced to show that the difference in the early stages depends on the presence or absence of bacteria rather than on the amount of injury to the tissue, whereas those differences in the later stages result from the degree of injury to the tissue rather than from the nature of the agent which produced the injury.

AUTHOR'S SUMMARY (B. M. FRIED).

ROENTGEN RAY NECROSIS OF THE MANDIBLE. H. RAHM, *Strahlentherapie* **25**:338, 1927.

A patient who was operated on in July, 1920, for carcinoma of the lower lip, during the following year received seven erythema doses through a 0.5 mm. zinc filter over the mandible. Epilation followed, and two years later a slight induration of the skin could be noticed. In February, 1926, the left side of the face swelled; for three days the patient had a high temperature, then an abscess opened spontaneously in the mandibular region. Roentgen-ray examination revealed a process in the mandible similar to osteomyelitis. In the absence of any other explanation, a diagnosis of a late roentgen-ray necrosis was made. As practical conclusion, the author emphasizes that not more than a 100 per cent erythema dose should be given to the bone of adults at one time and from 300 to 400 per cent erythema dose as total treatment, with a six months interval.

E. A. POHLE.

PROLIFERATIVE REACTIONS OF THE THYMUS. V. WITUSCHINSKI, *Virchows Arch. f. path. Anat.* **262**:595, 1926.

The reactions set up in the thymus by the presence of aseptic foreign bodies were studied in young cats and rabbits. The immediate change which resulted from the introduction of the foreign body, a spicule of celloidin, was necrobiosis of the lymphoid cells. Within seven hours, the cells of the epithelial reticulum became enlarged and phagocytized the necrotic lymphocytes. This was followed by proliferation of the epithelial reticulum, of the periadventitial histocytes and, to a lesser degree, of the endothelium of the capillaries. The young epithelial reticulum cells differentiated into fibroblasts, as did also the histocytes, and formed a collagenous capsule about the foreign body. Histocytes and perhaps also young epithelial reticulum cells formed myelocytes and pseudo-eosinophilous granulocytes. Plasma cells were formed from the adventitial histocytes.

O. T. SCHULTZ.

ANOMALY OF THE CORONARY ARTERY. G. GRÄTZER, *Virchows Arch. f. path. Anat.* **262**:608, 1926.

In a woman dying at the age of 68 with symptoms of cardiac decompensation, the left coronary artery was absent, and the right was represented by three vessels, each of which opened into the right sinus of Valsalva by a separate ostium. The middle artery ran in the atrioventricular sulcus, and corresponded to the normal right coronary artery. The left vessel ran in the anterior longitudinal sulcus, its terminal distribution being formed by branches corresponding to those of the left coronary artery. The right vessel, which was the smallest of the three, ran to the apex of the right ventricle. The embryogenesis of the anomaly and of the collateral circulation which developed is discussed.

O. T. SCHULTZ.

THROMBOSIS OF THE RENAL VEIN. K. SCHRÖDER, *Virchows Arch. f. path. Anat.* **262**:634, 1926.

In four cases of thrombosis of the renal veins in infants, the process led to complete hemorrhagic infarction of the kidney. Ascending pyelonephritis was present in each case, and the inflammatory process was believed to have resulted in thrombosis of smaller intrarenal veins, from which the process was propagated backward into the main vessel. In three cases, the process occurred

on the right side, and in one it was bilateral. As proof that the thrombotic process begins in the small veins, the author describes a case of pyelonephritis in an infant, with multiple thrombosis of the smaller intrarenal veins, but without involvement of the main vessel. As an example of thrombosis originating in a larger vessel, the author includes a case of generalized tuberculosis in a child in whom intimal tuberculosis of a large medullary renal vein had led to thrombosis, but without complete infarction of the kidney. In a man, aged 79, with bilateral thrombosis of the renal veins, extending into the vena cava, the process was held to have started in multiple areas of damage to smaller veins within the kidney.

O. T. SCHULTZ.

PHLEBOSCLEROSIS. W. SCHILLING, *Virchows Arch. f. path. Anat.* **262**:658, 1926.

Patchy thickening of the vein wall occurs most frequently in the inferior cava and in the veins of the lower extremity, in areas subjected to mechanical stress. It is equally frequent in both sexes and increases in frequency with age. The process, which is identical with arterial atherosclerosis, is primarily a degenerative change of the intima, to which thickening of the media and adventitia is secondary. A true inflammatory reaction is rarely present and a causal relation of toxic or infectious agents could not be determined.

O. T. SCHULTZ.

AGRANULOCYTOSIS. H. BALTZER, *Virchows Arch. f. path. Anat.* **262**:681, 1926.

To the gradually increasing number of examples of the condition for which W. Schultz, in 1922, proposed the name "agranulocytosis," Baltzer adds three, which differ from the previously reported cases in that two occurred in young women and one in an old man, whereas most of the previously reported cases have been in women of middle age. In the three there was the usual necrotizing, ulcerative inflammation of the pharynx. The author considers the disease characteristic.

O. T. SCHULTZ.

SECONDARY MYELOSIS IN CARCINOMA. G. SEEMANN and A. KRASNOPOLSKI, *Virchows Arch. f. path. Anat.* **262**:697, 1926.

In a woman, aged 38, with diffuse carcinoma of the stomach, the erythrocyte count decreased progressively from 4,022,000 to 520,000. The leukocytes varied from 10,000 to 15,000, myelocytes, metamyelocytes, and promyelocytes constituting from 15 to over 22 per cent of the total. At necropsy, marked hemopoiesis was evident in the bone marrow, liver and spleen, leading in the latter two organs to the histologic picture of leukemia. In the spleen, the formation of hemocytoblasts from the sinus endothelium could be traced. The hemopoiesis is considered a regenerative process, and the similarity of the histologic changes to those in leukemia leads the authors to conclude that a distinction cannot be made between primary and secondary hyperplasia of the blood forming tissues, and that true leukemia is a secondary reactive process.

O. T. SCHULTZ.

PLACENTAL TRANSMISSION OF HODGKIN'S DISEASE. A. PRIESEL and A. WINKELBAUER, *Virchows Arch. f. path. Anat.* **262**:749, 1926.

Two weeks before the end of a normal pregnancy, painless enlargements of the superficial lymph nodes developed in a woman, aged 31. From the microscopic examination of an excised node, the diagnosis of lymphogranulomatosis was made. A nodular swelling was noted in the left supra-orbital

region of the child when the latter was 11 weeks old; the mother had died in the meantime and a necropsy had not been performed. The child died at the age of 4½ months. The characteristic histopathologic changes of lymphogranulomatosis were present in the bones of the skull, the bone marrow, the liver, the thymus and the retroperitoneal and mesenteric lymph nodes. The early onset of the disease in the child convinces the authors of the placental transmission of the process. Bacteriologic examinations and animal inoculations were negative for tuberculosis.

O. T. SCHULTZ.

PATHOGENESIS OF THE CIRRHOSIS OF THE LIVER. S. M. ZYPKIN, *Virchows Arch. f. path. Anat.* **262**:791, 1926.

Zypkin describes the histologic changes in the liver and spleen in nine cases of obstructive jaundice with a duration varying from one month to two and one-half years. The fibrosis about the bile ducts and their radicles is not secondary to the degenerative changes and necrosis of the parenchyma of the liver, which occur early in obstructive jaundice but which were still present in his case of longest duration. He believes that the noxious agent—in obstructive jaundice, the retained bile—acting locally, causes, at the same time and primarily, both parenchymatous degenerative changes and hyperplasia of connective tissue. He devotes considerable discussion to the general concept that harmful agents acting on any tissue cause primarily both degenerative alterations in the parenchyma and hyperplasia of the stroma. If the noxa acts generally through the blood stream, a third element is added—hyperplasia of lymphadenoid tissues, which is manifested chiefly in the spleen and bone marrow. Applying this conception to cirrhosis of the liver and to the splenomegaly which may accompany it, he attempts to explain the course of events in those forms of cirrhosis in which the harmful agent acts locally, through the bile ducts as in biliary cirrhosis, through the portal system as in Laennec's cirrhosis or through the hepatic vascular system as in the cirrhosis of passive congestion. In these forms the spleen is small, or it may be only slightly enlarged, as the result of passive congestion. If the noxious agent is present in the general circulation, it causes a more diffuse stroma hyperplasia and more widespread parenchymatous changes, the latter sometimes including hypertrophy and proliferation of liver cells and the process resulting in the Hanot hypertrophic form of cirrhosis, which is always associated with splenomegaly; or the form of Laennec's atrophic cirrhosis in which the fibrosis is so diffuse that it has been considered by some an end-stage of the Hanot form, this variety being also associated with splenomegaly and being the result of a factor which acts locally through the portal circulation and diffusely through the general circulation. The splenomegaly is due in part to pulp hyperplasia, which is one of the triad of general reactions, and in part to stroma hyperplasia. The Banti form of splenomegaly with cirrhosis is also fitted into the scheme, the anemia which occurs in this condition being the result of a more strongly acting general factor which causes hyperplasia and embryonic dedifferentiation of the bone marrow. The clinical improvement which follows splenectomy, not only in Banti's disease but in a variety of other conditions, is explained on the theory that the spleen enhances the activity of noxious agents present in the general circulation. According to Zypkin, the classification of the cirrhoses of the liver should be simplified by the formation of only two categories, cirrhosis without splenomegaly, which is due to a locally acting agent, and cirrhosis with splenomegaly, which is due to a diffusely acting agent.

O. T. SCHULTZ.

MUCOID CARCINOMA OF TONGUE. P. KAMPRATH, *Virchows Arch. f. path. Anat.* **263**:1, 1927.

A tumor removed from the tongue of a woman, aged 68, contained glandular alveoli lined by cylindric cells and filled with mucus, and areas of squamous cell epithelioma. The tumor is believed to have arisen from mucous glands of the tongue, the squamous portion having been derived from indifferent epithelial cells.

O. T. SCHULTZ.

XANTHOMATOUS FIBROSARCOMA OF THE STOMACH. A. UCKE, *Virchows Arch. f. path. Anat.* **263**:25, 1927.

A slowly growing tumor of the stomach, which invaded the peritoneum, liver and pancreas, was composed of elongated spindle cells, between which were large, round, foam cells of xanthoma type. The latter were held to be histiocytes filled with lipid material.

O. T. SCHULTZ.

LIPOID DEPOSITION IN THE EYE. A. A. KOLEN, *Virchows Arch. f. path. Anat.* **263**:46, 1927.

Small amounts of deposited lipid material appear in the tissues of the eye as early as the age of 10 years, and the process becomes more marked with advancing age. The material is present in largest amounts in the ciliary body and sclerocorneal junction, where it leads to the formation of the arcus senilis. It is present also in the sclera and choroid. The increase of lipid material in the eye with age runs parallel with the increase of the material in the other fibro-elastic tissues of the body. The ocular lipoidosis does not have any apparent effect on vision.

O. T. SCHULTZ.

REDUPLICATION OF URETERS. C. VAN GELDEREN, *Virchows Arch. f. path. Anat.* **263**:89, 1927.

To the reported examples of complete bilateral reduplication of the ureters, the author adds three which conformed to the Weigert rule that the more caudal or mesial ureteral opening into the bladder belong to the superior pelvis.

O. T. SCHULTZ.

CONGENITAL DIVERTICULUM OF THE URINARY BLADDER. S. USAMI, *Virchows Arch. f. path. Anat.* **263**:99, 1927.

Usami makes a case of diverticulum of the urinary bladder in an adult the basis of a discussion of the differences between acquired and congenital diverticula. The latter are divided into those that are present at birth and those that develop later on the basis of a congenital factor, one of the commonest of which is constituted by accessory embryonic ureteral remnants within the bladder wall. In Usami's case there was a large diverticulum occupied by a stone, three smaller intramural diverticula and numerous areas in which the mucosa dipped down between the muscle bundles. Urinary retention was not present to explain the conditions seen, which were believed to be the result of a developmental anomaly of the bladder. In support of this view was the presence within one intramural ureteral sheath of a small, epithelial lined ductlike passage, which was interpreted as a rudimentary accessory ureter.

O. T. SCHULTZ.

CONGENITAL ANOMALY OF THE HEART WITH TRANSPOSITION OF THE ARTERIAL TRUNKS. H. WURM, *Virchows Arch. f. path. Anat.* **263**:123, 1927.

Wurm describes the heart of a 3 months old boy which was characterized by transposition of the arterial trunks, the aorta being to the left anteriorly and

arising from a small left ventricle with tricuspid valve, the pulmonary artery being to the right posteriorly and arising from a large right ventricle with a bicuspid valve. The ventricular septum was defective. The foramen ovale was patent and there was coarctation of the aorta. The author attempts to explain the genesis of the anomaly according to the Spitzer phylogenetic theory of incomplete torsion or detorsion of the arterial end of the primitive cardiac tube, according to which, transposition of the arterial trunks is not a true transposition, and the apparent transposition of the ventricles in such conditions is a corrective process. Wurm interprets his case as a true transposition resulting from situs inversus of the bulboventricular part of the heart. Spitzer, in an article which follows that of Wurm, attempts to show that the reported anomaly is the result of detorsion and that the condition present is not an actual transposition. The difference in the two opinions depends apparently on differences in interpretation of the nature of certain structures present, and especially on whether a portion of the defective septum is to be considered an aorticopulmonary crest.

O. T. SCHULTZ.

TRANSPOSITION OF AORTA AND PULMONARY ARTERY. F. HOGENAUER, Virchows Arch. f. path. Anat. **263**:174, 1927.

An example of transposition of the aortic and pulmonic trunks of the heart of a child who died at the age of 2 months is explained on the basis of Spitzer's theory of incomplete torsion of the primitive cardiovascular tube, with persistence of the phylogenetic right-sided aorta.

O. T. SCHULTZ.

POSTMORTEM RHYTHMIC CONTRACTION OF THE HEART. F. POLSTORFF, Virchows Arch. f. path. Anat. **263**:179, 1927.

In the course of a necropsy done nine hours after death on a man, aged 57, rhythmic contractions of the right auricular appendage of the heart occurred at the rate of from 50 to 60 per minute on removal of the heart. The contractions lasted ten minutes and could be reestablished by stroking the auricle with the point of a knife. The rest of the heart did not participate in the contractions. Postmortem contraction of the heart of fetuses and new-born infants is not infrequent and is probably to be explained by the automaticity of the fetal organs, but the phenomenon is rarer when death occurs at any appreciable time after birth; the abstractor has seen one striking example of the phenomenon. The author concludes that none of the theoretical or experimental attempts to explain postmortem cardiac rhythmicity is satisfactory.

O. T. SCHULTZ.

LIPOID DEPOSITION IN TENDONS. N. KUSNETZOWSKY, Virchows Arch. f. path. Anat. **263**:205, 1927.

In experimental hypercholesterolemia of rabbits, only slight deposition of lipoids occurred in the achilles tendon. When the tendon was injured, however, a heavy deposition developed in young connective tissue cells about and within the tendon, such cells being transformed into xanthoma cells. The similarity of this condition to the xanthomatous granulomas and tumors of tendon sheaths of human beings is emphasized.

O. T. SCHULTZ.

INTESTINAL ANTHRACOSIS. F. MATAKAS, Virchows Arch. f. path. Anat. **263**:220, 1927.

In a study of the localization of carbon pigment in the intestine, Matakas examined the Peyer's patches of 650 necropsies at all ages and selected for

further microscopic study only those cases in which pigmentation could be detected by the naked eye. In 183 necropsies, pigment identified as carbon was present in 44 per cent. The material was present within spindle cells, usually at the base of the lymphoid follicles, and more rarely at the base of the mucosa or in the interfollicular tissue. It may be present at so early an age as 6 months. The pigment is believed to be derived from swallowed material, rather than by a retrograde process from intestinal organs which have become secondarily pigmented from the mediastinal glands. Anthracosis of mesenteric lymph nodes is secondary to intestinal deposition. The punctate areas of pigmentation so frequently seen in the Peyer's patches and solitary follicles are due to hemosiderin.

O. T. SCHULTZ.

OCCUPATIONAL SILICOSIS. V. M. KOGAN-JASNY, *Virchows Arch. f. path. Anat.* **263**:234, 1927.

Attention is directed to a condition of universal silicosis in workers in an electrical manufactory, whose occupation consisted of the splitting of mica into thin sheets. The discussion is largely clinical, the symptomatology consisting of lassitude, headache, dizziness, loss of hair, dryness of buccal and upper respiratory mucosa, rhinitis and laryngitis, dyspnea, gastric subacidity, anemia and menstrual disturbances. The subcutaneous tissue removed by biopsy in two cases was the seat of a granulomatous reaction due to a foreign body, similar to that which occurs about unabsorbed oil. The excretion of silicic acid in the urine was increased. The disease process resulting from the material taken in by way of the respiratory, digestive and cutaneous systems is due, not to the mechanical action of insoluble particles, but to the diffuse reaction of all the tissues of the body to the chemical action of absorbed colloidal silicic acid.

O. T. SCHULTZ.

PERIARTERITIS NODOSA. P. GOHRBANDT, *Virchows Arch. f. path. Anat.* **263**:246, 1927.

Gohrbandt describes the microscopic anatomy of five cases of periarteritis nodosa, in three of which the lesions were recent, and in two, older and healed. The process began in the vasa vasorum, led first to exudation and leukocytic infiltration, then to eosinophilous and lymphocytic infiltration, which became especially marked in the peri-adventitial tissue, and, finally, to a proliferative reaction which involved the entire wall as well as the surrounding tissue. Late stages were characterized by marked fibrotic thickening of all the arterial coats. Bacteria were not found, and the condition was considered a nonspecific, infectious-toxic involvement of the arterial system which led to characteristic changes in the arterial wall.

O. T. SCHULTZ.

CELLULAR INCLUSIONS IN THE OVARY. H. O. NEUMANN, *Virchows Arch. f. path. Anat.* **263**:274, 1927.

To a previously reported example of the presence of misplaced chromaffin tissue in the hilus of the ovary, Neumann adds a second case in which the ovary contained small groups of closely placed, ovoid cells, with small, deeply stained nuclei. A chromaffin reaction was not obtained in this later case, but the author believes that the misplaced cells in both cases were derived from the sympathetic tissue which normally give rise to the suprarenal medulla and other paraganglionic structures.

O. T. SCHULTZ.

ANATOMIC CHANGES IN LATHYRISM [LUPINOSIS]. I. N. FILIMONOFF, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **105**:76, 1926.

Lathyrus or chick-pea poison has a high affinity for certain parts of the central nervous system and causes a spastic inferior paraplegia from pyramidal degeneration. As the duration of life is not shortened, the literature contains the record of only one autopsy in such cases. Filimonoff reports the case of a man who acquired the disease in the Russian epidemic of 1892-1893, suffered from spastic general paralysis of the lower extremities and other symptoms for thirty years and then died from acute lymphatic leukemia. The spinal cord was reduced in size in the thoracic and lumbosacral regions, sclerosis was seen in the pyramidal tracts and degeneration of the nerve cells occurred in the corresponding cortex of the brain.

WILLIAM HUEPER.

A CARCINOMA OF THE CHOROID PLEXUS OF THE FOURTH VENTRICLE. A. ESSER, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **106**:511, 1926.

The author describes a papillary carcinoma of the choroid plexus composed of rounded and cubical cells without basal processes, infiltrating and not metastasizing. He considers his case the fifth one reported (apparently not including the American literature).

ROY GRINKER.

CHOLELITHIASIS AND CARCINOMA OF THE GALL-BLADDER. E. LUELSDOFF, *Ztschr. f. Krebsforsch.* **24**:395, 1927.

From a statistical study of the literature and of the necropsy material of the Barmbeck Hospital in Hamburg, the author finds a parallel relationship between cholelithiasis and carcinoma of the gallbladder and biliary passages. Although the statistical method cannot decide definitely whether stone is the cause or the result of the carcinoma, the author believes that the frequent association and the precancerous changes described by him in one gallbladder indicate a causal relation of the calculus to the neoplasm.

O. T. SCHULTZ.

HORNIFYING CARCINOMA OF THE STOMACH. F. BÖDECKER, *Ztschr. f. Krebsforsch.* **24**:406, 1927.

To the small number of previously reported human cases of carcinoma of the stomach with keratinizing epithelium, the author adds two and describes the cytology of the neoplasms in detail. In each there were typical glandular carcinomatous areas and others composed of hornified epithelium of squamous type, for which reason the name adenocarcinoid was chosen. In one case there was also a cylinder cell carcinoma of the colon, which was held to be an independent primary tumor. For the origin of tumors of the gastro-intestinal tract containing heterologous epithelium, the author considers the embryonic misplacement of squamous epithelium or metaplasia through a stage of dedifferentiation with subsequent differentiation into squamous epithelium as less probable explanations than the heteroplasia doctrine of Schridde, according to which, indifferent entodermal cells retain the potentiality of differentiating at some later period of life into epithelia of various types.

O. T. SCHULTZ.

ECHINOCOCCOUS AND CARCINOMA OF THE LIVER. E. ZIEGLER, *Ztschr. f. Krebsforsch.* **24**:425, 1927.

Three examples of carcinoma of the liver associated with echinococcal disease of the same organ are described. The author concludes that the reactions of the liver to an echinococcal cyst are precancerous in nature and that the chronic inflammatory process acts as an irritant which may lead to carcinoma.

O. T. SCHULTZ.

Microbiology and Parasitology

PUERPERAL INFECTION DUE TO ANAEROBIC STREPTOCOCCI. O. H. SCHWARZ and W. J. DIECKMANN, *Am. J. Obst. & Gynec.* **13**:467, 1927.

Culturing the blood following chills, and the lochia by means of Little's tube, Schwarz and Diekmann frequently recovered an anaerobic streptococcus which seemed to be identical to the organism described by Schottmüller as *Streptococcus putridus*. The case histories and autopsies were detailed in five cases in which this organism was isolated in pure culture. A. J. KOBAK.

PULMONARY SPIROCHETOSIS. CURTIS E. SMITH and G. Y. RUSK, *Am. J. Path.* **3**:225, 1927.

All forms of pulmonary spirochetosis are regarded as due to secondary infection. The frequent association of fusiform bacilli with spirochetes in pulmonary abscess and gangrene suggests that it may concern invasion by organisms of the Vincent type.

PFEIFFER REACTION WITH LEPTOSPIRA IN YELLOW FEVER. A. W. SELLARDS, *Am. J. Trop. Med.* **7**:71, 1927.

The serum from eleven patients examined about three and one-half months after recovery from typical yellow fever gave negative Pfeiffer reactions to *Leptospira icteroides* and *Leptospira icterohaemorrhagiae*. As controls for these negative tests, the serum of two guinea-pigs immune to *L. icterohaemorrhagiae* gave positive Pfeiffer reactions with *L. icteroides* and *L. icterohaemorrhagiae*. These results, therefore, furnish addition evidence of the identity of *L. icterohaemorrhagiae* and *L. icteroides*.

A striking characteristic of leptospiral infections is the development and persistence in the blood of immune substances which are easily demonstrable by the Pfeiffer phenomenon; these eleven cases of yellow fever failed to show this phenomenon, and it is one which is vital for the acceptance of *L. icteroides* as the etiologic agent of yellow fever. Nevertheless, this failure leads to certain constructive considerations.

The lack of any etiologic relationship of *L. icteroides* to yellow fever is of definite significance in determining public health measures for the control of this disease. If *L. icteroides* were the causative agent of yellow fever, we would be confronted with the possibility of an almost unlimited animal reservoir in rodents under circumstances that would be discouraging for the ultimate extermination of yellow fever from a community.

The occurrence of negative Pfeiffer reactions in typical cases of yellow fever facilitates the problem of determining the nature of the disease described in Africa as yellow fever. From time to time serious doubt has been expressed as to whether true yellow fever occurs in Africa, although cases have been described which clinically and pathologically are characteristic. A negative Pfeiffer reaction with leptospira definitely tends to confirm rather than to refute the diagnosis of yellow fever.

Some important questions are brought into sharp relief. Investigations from various countries make it evident that leptospiral infections are primarily a disease of rodents with occasional off-shoots in man, notably in the form of Weil's disease, but not as yellow fever. It becomes necessary to review anew the evidence of the susceptibility to yellow fever of the guinea-pig, mouse, rat, dog and monkeys as tested by the injection of *L. icteroides* or of specimens of blood from cases of yellow fever. One must give serious consideration to the older view that the virus of yellow fever is limited in nature to its cycle in man and in the mosquito.

AUTHOR'S SUMMARY.

STUDIES ON PERITONITIS. B. STEINBERG and H. GOLDBLATT, Arch. Int. Med. **39**:449, 1927.

Both the blood and the lymph of normal dogs were bacteria-free whether the animals had been fed or had fasted. Following the intraperitoneal injection of *Bacillus coli* suspended in physiologic salt solution, a large number of these organisms were found in the lymph (thoracic duct), and a relatively smaller number in the blood. When dogs with the thoracic duct intact received intraperitoneal injections with saline suspensions of *B. coli*, they rapidly developed a severe bacteremia, but practically always survived. Following the intraperitoneal injection of *B. coli* suspended in gum tragacanth, a small number of the organisms appeared in the lymph (thoracic duct), but none was detected in the blood. When dogs with the thoracic duct intact received intraperitoneal injections of *B. coli* suspended in gum tragacanth, they did not have bacteremia; yet these animals invariably died. Bacteremia is not responsible for the death of dogs in acute *B. coli* peritonitis. The rapid passage of bacteria from the peritoneal cavity into the blood was associated with the recovery of the animal.

AUTHOR'S SUMMARY (S. A. LEVINSON).

NERVOUS COMPLICATIONS OF VARIOLA, VACCINIA AND VARICELLA. R. E. WILSON and F. R. FORD, Bull. Johns Hopkins Hosp. **40**:337, 1927.

A diffuse nonsuppurative encephalomyelitis occurs as a rare but specific complication of variola, vaccinia and varicella. In cases associated with vaccinia, vaccine virus has been demonstrated in the nervous tissues. As yet anatomic studies apparently have not been made on encephalomyelitis associated with varicella (no deaths in twelve cases). It is possible that cases of encephalomyelitis in vaccinia have been mistaken for tetanus.

THE OCCURRENCE OF STAPHYLOCOCCUS AUREUS INFECTION WITH A SCARLATINI-FORM RASH. FRANKLIN A. STEVENS, J. A. M. A. **88**:1957, 1927.

An exanthem may accompany *Staphylococcus aureus* infection. This exanthem is distinguished with difficulty from the rash occurring during infections with *Streptococcus scarlatinae*. Cases of staphylococcus infection may be distinguished by the absence of scarlatinal streptococcus, the presence of the staphylococcus and positive blanching phenomena with staphylococcus antitoxic serum.

UREA-SPLITTING BACTERIUM IN INTESTINAL TRACT OF CHILDREN. J. V. COOKE and H. R. KEITH, J. Bact. **13**:315, 1927.

Bacterium ammoniagenes is the name suggested for a bacterium having exceptional power to split ammonia from urea.

STUDIES ON BACTERIAL ENZYMES. JAMES M. NEILL and WILLIAM L. FLEMING, J. Exper. Med. **45**:937 and 947, 1927.

Bacillus botulinus produces a maltase and a lipase, the first being endocellular and the second extracellular. The carbohydrates of the Welch bacillus remain active in sterile solutions of the bacterial cells.

NUCLEAR INCLUSIONS PRODUCED BY VARICELLA VIRUS IN THE TESTICLES OF MONKEYS. THOMAS M. RIVERS, J. Exper. Med. **45**:961, 1927.

Nuclear inclusions were not found after the inoculation of virus and convalescent serum, but they were found after the inoculation of virus and non-immune serum. The inoculation of one testicle with virus prevented the

formation of nuclear inclusions in the other one after later inoculation with the same virus. These results show that the inclusions are specific and, furthermore, that animals are susceptible to the virus of varicella.

THE VIRUS OF VESICULAR STOMATITIS OF HORSES. PETER K. OLITSKY, J. Exper. Med. **45**:969, 1927.

This virus is similar to that of foot-and-mouth disease, but the two viruses do not have any generic relation to the herpetic virus. Experiments with ultraviolet light indicate that the virus of stomatitis is similar to bacterial protoplasm.

GROWTH REQUIREMENTS OF HEMOPHILIC BACILLI. FRANCIS C. O. VALENTINE and THOMAS M. RIVERS, J. Exper. Med. **45**:993, 1927.

The majority of the nonhemolytic strains require the addition of both X and V to the medium, while a few need only V; however, most hemolytic strains require only V, but some need both V and X.

A SIMPLE METHOD OF ISOLATING PURE CULTURES FROM SINGLE BACTERIAL CELLS. ROY C. AVERY and STANLEY J. LELAND, J. Exper. Med. **45**:1003, 1927.

The principle of this method is to grow bacteria in a thin film of medium on a cover glass with numbered squares, following the growth of one or more single bacterial cells until a colony large enough for transplants has formed. The method is a modification of Hansen's method for isolating pure cultures of yeasts.

ELIMINATION OF TUBERCLE BACILLI IN THE FECES, BILE AND URINE OF INFECTED GUINEA-PIGS. DAVID PERLA, J. Exper. Med. **45**:1025, 1927.

Tubercle bacilli may be eliminated in the feces, bile and urine of tuberculous guinea-pigs. After intraperitoneal inoculation, the bacilli may appear in the feces and persist for about one week.

BACTERIOPHAGE FROM THE COMMON HOUSE FLY. RICHARD E. SHOPE, J. Exper. Med. **45**:1037, 1927.

Bacteriophage which was active against four species of bacteria was found in an extract in salt solution of house flies. At the same time, a growth inhibiting principle against four other species of bacteria was found in the same extract. These two activities appear to be unrelated.

AN INVESTIGATION ON THE PRODUCTION OF *B. ABORTUS* AGGRESSIN. S. J. SCHILLING and WILLIAM L. BLEECKER, J. Infect. Dis. **40**:469, 1927.

The injection of a suspension of virulent *B. abortus* into the peritoneal cavity of guinea-pigs resulted in the early death of the animals with accumulation of purulent exudate in that cavity. Guinea-pigs after injections simultaneously with the centrifugalized and phenolized exudate, and with a suspension of live cultures, presented at two and four weeks no more marked progression of the inoculation disease than guinea-pigs receiving live cultures only; animals receiving larger doses of exudate showed no more advanced pathologic changes than those receiving less. Thus no aggression action was observed. Guinea-pigs given injections with exudate and two weeks later inoculated with live cultures showed no evidence of immunization. This also indicates that the exudate probably contained no aggressin.

AUTHORS' SUMMARY.

MAGNESIUM AMMONIUM PHOSPHATE CRYSTALS IN AEROBIC CULTURES OF *BRUCELLA ABORTUS* AND *BRUCELLA MELITENSIS*. I. FOREST HUDDLESON and O. B. WINTER, J. Infect. Dis. **40**:476, 1927.

From observations on the growth of *Brucella abortus* and *Brucella melitensis* on the medium described in this paper and from the examination of crystals, the following conclusions are drawn: The crystals are magnesium ammonium phosphate ($\text{Mg NH}_4 \text{PO}_4 \cdot 6\text{H}_2\text{O}$), and their large size and well developed shape are due to their slow formation in a semisolid medium (a gel). The increase in the p_{H} of the medium and the separation of the crystals are due to the formation of ammonia produced by the activity of the organisms in question on the culture medium. The formation of this salt interferes with the viability of *Bacterium abortus* and *Brucella melitensis*.

AUTHORS' SUMMARY.

THE RELATION OF HYDROLYTIC DECOMPOSITION PRODUCTS OF PROTEINS TO BACTERIAL GROWTH. G. J. HUCKER and D. C. CARPENTER, J. Infect. Dis. **40**:485, 1927.

The amount of nitrogen available for bacterial growth shows considerable variation during the digestion process of proteins when determined by noting the minimum amount necessary to produce a visible growth of certain test organisms. There appears to be no relationship between the amount of free amino nitrogen present and the ability of partially digested proteins to produce bacterial growth. There usually appears, following about the sixth to the eighth hour of the digestion, a period when relatively large amounts of the digest are required to promote growth. Earlier in the digestion and also after this period, the percentage of protein necessary for growth is much smaller. Although the original protein may have some effect on the amount of available nitrogen for bacterial growth in the digest, the stage of the digestion is also an important factor.

AUTHORS' SUMMARY.

THE INFLUENCE OF PURULENT INFECTION ON THE DEVELOPMENT OF EXPERIMENTAL SCURVY. HENRY L. JAFFE, J. Infect. Dis. **40**:502, 1927.

Six of eleven infected guinea-pigs on a scurvy diet developed severe purulent infections and did not develop scurvy within from nineteen to forty days. Uninfected guinea-pigs on the same diet developed scurvy in from thirteen to eighteen days. The injection of *Staphylococcus albus* into animals with early signs of scurvy caused a rapid fatal termination. The course of scurvy was not influenced by the injection of standard staphylococcus vaccine. These studies suggest the possibility that antiscorbutic substances may be developed by bacterial growth in the tissues or as a result of the action of absorbed toxins on the internal organs.

AUTHOR'S SUMMARY.

LEPTOSPIRA BIFLEXA (WOLBACH AND BINGER, 1914. EMEND. NOGUCHI, 1918). VLADIMIR T. DIMITROFF, J. Infect. Dis. **40**:508, 1927.

Leptospira biflexa is widely distributed in potable waters in Eastern United States. It was found in 69 per cent of all water samples examined and in 87.5 per cent of municipal drinking water from forty-seven cities. There is no reason to believe that the European water leptospiras represent a different species. This wide distribution and the value of feces in initial culture suggests that like the colon bacillus one of the natural habitats of this genus is in the intestinal tract of animals. If the rules of nomenclature permitted, *Leptospira communis* would be an appropriate name.

This leptospira is not pathogenic for mice and guinea-pigs. It does not protect against infection with *Leptospira icterohemorrhagiae*. The value of filtration through candles made of diatomaceous earth is established as a useful procedure as an aid to their isolation in pure culture.

AUTHOR'S SUMMARY.

GROWTH OF CL. BOTULINUM AND CL. SPOROGENES IN VEAL INFUSION BROTH UNDER REDUCED PRESSURE. GAIL M. DACK, W. A. STARIN and MARIE WERNER, J. Infect. Dis. 40:525, 1927.

The degree of anaerobiosis is a factor influencing the delayed germination of the spores of *Clostridium botulinum* types A and B; oxygen pressures of 5 cm. completely inhibit the growth of *Clostridium botulinum* types A and B and *Clostridium sporogenes*. The organisms grow at 50 cm. pressure of carbon dioxide and, at this pressure, toxin of a high titer is produced by *Clostridium botulinum* types A and B.

AUTHORS' SUMMARY.

SPONTANEOUS INFECTIONS OF GUINEA-PIGS. PNEUMOCOCCUS, FRIEDLÄNDER BACILLUS AND PSEUDOTUBERCULOSIS (EBERTHELLA CAVIAE). ARNOLD BRANCH, J. Infect. Dis. 40:533, 1927.

Fifty-six cases of Friedländer bacillus and thirty-six cases of pneumococcus group 4 infections in guinea-pigs are described; the lesions included septicemia, sinusitis, otitis, pneumonia, pleurisy, pericarditis, peritonitis, metritis, cellulitis and focal abscesses. The Friedländer organism belongs to type B in Julianelle's classification, i. e., that group which cross agglutinates with type 2 pneumococcus antiserum. The pneumococcus does not agglutinate with antisera of any of the fixed types but is related serologically by its protein fraction with human strains. The frequency of spontaneous chronic infections in guinea-pigs is stressed and the possible effect these may have on altering the resistance of the infected animal to subsequent experimental inoculations with tubercle bacilli is discussed. The point of entry in the majority of instances appears to be by the upper respiratory tract and middle ear, and the necessity of examining the sinuses and ears at necropsy is emphasized. Fourteen cases of pseudotuberculosis are described. Twelve of these were associated with *Eberthella caviae* of Bergey's classification, and some experimental evidence is afforded that it is the specific infective agent and that infection can occur by feeding. Caution is advised in diagnosing tuberculosis by gross inspection alone.

AUTHOR'S SUMMARY.

RHEUMATIC FEVER: BACTERIOLOGIC STUDIES OF A NONMETHEMOGLOBIN-FORMING STREPTOCOCCUS WITH SPECIAL REFERENCE TO ITS SOLUBLE TOXIN PRODUCTION. KONRAD E. BIRKHAUG, J. Infect. Dis. 40:549, 1927.

A new species of a nonmethemoglobin-forming inulin-fermenting bile-insoluble and toxigenic, gram-positive streptococcus was regularly isolated from the tonsillar crypts and abscesses, and irregularly from blood cultures, heart vegetations, feces and urine, of persons stigmatized by rheumatic fever and its syndromes.

Culturally, toxigenically and serologically, the nonmethemoglobin-forming streptococci constitute a closely related group of micro-organisms, distinguishable biologically from the groups of *Streptococcus viridans* and *Streptococcus hemolyticus*.

In a study of the production of soluble toxins by streptococci isolated from patients with rheumatic fever, it was found that among ninety-eight strains of *Streptococcus hemolyticus*, toxin was not demonstrated; among two hundred and

forty-seven strains of *Streptococcus viridans*, 4.7 per cent produced toxin and among sixty-eight strains of the nonmethemoglobin-forming streptococcus, 7 per cent were found to produce a soluble toxic filtrate, slightly weaker in potency than that produced by the *Streptococcus scarlatinae* and *Streptococcus erysipclatis*.

When injections were made intradermally with 0.1 cc. of a 1:10 dilution of the toxic filtrate of the nonmethemoglobin-forming streptococcus, 18 per cent of normal adults and 11 per cent of normal children without a history of rheumatic fever, gave positive skin reactions measuring more than 1 cm. in diameter within twenty-four hours after the injection.

Among persons with a definite history of rheumatic fever and its syndromes, when tested intradermally with 0.1 cc. of a 1:100 dilution of the soluble toxic filtrate produced by the nonmethemoglobin-forming streptococcus, 56 per cent of adults and 76 per cent of children gave positive skin reactions, and when tested with 1:10 dilution of the toxin, 67 per cent of adults and 85 per cent of children reacted positively with lesions measuring more than 1 cm. in diameter within twenty-four hours after the injection.

Intramuscular injections of increasing doses of the toxic filtrate in laboratory animals and in human beings susceptible to the toxin produced a neutralizing antitoxin.

Injected intravenously and subcutaneously in rabbits, the nonmethemoglobin-forming streptococcus invariably produced nonsuppurative polyarthritis, subacute bacterial endocarditis, myocarditis and epicarditis, with unique tendency to mitral stenosis, extensive mural vegetations and, occasionally, myocardial degeneration, with nodular cellular arrangements of multinuclear forms, as well as polymorphonuclear and mononuclear cells.

Injection intra-articularly and intramuscularly of large doses of the soluble toxic filtrate of the nonmethemoglobin-forming streptococcus in the author, who previously had repeatedly given a strongly positive intradermal reaction with 0.1 cc. of a 1:100 dilution of the toxin, produced a typical clinical picture of acute polyarthritis of the rheumatic type, which healed without suppuration or injury to the articular surfaces.

AUTHOR'S SUMMARY.

CLASSIFICATION OF BACTERIUM COLI BASED ON THE STUDY OF SEVENTY-FIVE VARIETIES. BRUNO LEO MONIAS, J. Infect. Dis. 40:570, 1927.

The first group, *Bacterium coli*, is characterized as follows: gram-negative, motile, peritrichous flagella, coagulation of milk and fermentation of lactose.

The examination of seventy-five strains gives two subdivisions: Strains that produce indol and creatine (*Bacterium indolicum*) and strains without these qualities (*Bacterium anindolicum*). Further subdivisions in both of these groups may be made according to their ability to ferment carbohydrates: varieties communior, commune, aerogenes and acidilactici corresponding to Jackson's nomenclature.

A second group, *Bacterium anaerogenes*, is characterized by the same qualities as the group, *Bacterium coli*, but differs in inability to produce gas from carbohydrates. There are four subdivisions in this group, according to the ability to produce indol and creatine and to coagulate milk or the partial or total inability to do so. This forms a transition group between *Bacterium coli* and *Bacterium enteritidis*.

The third group, *Bacterium enteritidis*, differs from *Bacterium coli* by the lack of power to coagulate milk and to ferment lactose. In this group as in the group *Bacterium coli* two subdivisions are found: one with the production of indol and creatine and the other without. In each of these groups there are again four classes, A, B, C and D, according to the fermentation of saccharose, raffinose and dulcitol.

AUTHOR'S SUMMARY.

SEWAGE FILTRATE AS A SOURCE OF BACTERIOPHAGE. JANET ANDERSON CALDWELL, J. Infect. Dis. 40:575, 1927.

Sewage filtrate, as tested with sixty-seven strains of gram-negative organisms, yields a potent bacteriophage for practically all strains of *Bacillus coli* isolated from urinary infections and for most of the other common gram-negative bacilli encountered in human diseases.

The use of sewage filtrate as a source of bacteriophage will materially increase the number of patients with urinary infections who can be treated with the bacteriophage; and will avoid confusion in the identification of resistant strains of bacteria.

THE PERSISTENCE OF BOTULINUM TOXIN IN DISCARDED CANNED FOODS. WILLIAM A. STARIN, J. Infect. Dis. 40:579, 1927.

Both the A and B types of *Clostridium botulinum* are capable of producing toxin in corn, peas and salmon, that will withstand exposure to drying, light—both diffuse and direct—and seasonal variations of temperature for a period of at least ninety days.

The toxin present after such prolonged exposure is the persisting original toxin, and not one newly formed as the result of the metabolism of *Clostridium botulinum* that may have been present in the original material, or that may have been introduced subsequently as a contaminant.

Putrefaction of vegetables and meats which were originally highly toxic does not cause a disappearance of the toxin. Peas, corn and salmon, exposed in a moist condition and highly contaminated with putrefactive organisms, yielded botulinum toxin after an interval of 122 days.

AUTHOR'S SUMMARY.

IMPERMEABILITY OF THE SMALL INTESTINE OF RABBITS OF BOTULINUM TOXIN. GAIL M. DACK and WILLIAM L. WOOD, J. Infect. Dis. 40:585, 1927.

The duodenum and ileum of the rabbit were found not to be permeable to botulinum toxin under the conditions of the experiments. Some toxin was demonstrated in the blood from the duodenum after sixty minutes, but not more than was found in the heart blood at the end of the experiment.

AUTHORS' SUMMARY.

SURFACE TENSION STUDIES WITH LACTOBACILLUS ACIDOPHILUS AND LACTOBACILLUS BULGARICUS. NICHOLAS KOPELOFF and PHILIP BEERMAN, J. Infect. Dis. 40:656, 1927.

Within the limitations of the experimental material under consideration the following points have been established:

A standardized method for determinations of surface tension on lactobacilli has been described and applied to twelve different strains of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*. With sodium ricinoleate three strains of *L. acidophilus* of proved therapeutic value grew in a medium depressed below 36 dynes, while two strains of *L. bulgaricus* proved by us incapable of intestinal implantation were inhibited at 43.2 dynes. The average critical point for all cultures labelled *L. acidophilus* was 37.9 dynes and for *L. bulgaricus*, 43.6 dynes. With sodium oleate, *L. acidophilus* grew to 23.8 dynes, while *L. bulgaricus* was inhibited at 41 dynes. The surface tension of inoculated and incubated cultures is higher than that of uninoculated controls kept in the icebox.

Tests of surface tension on lactobacilli compare favorably with sugar fermentation but offer a more accurate method of differentiation, agree with clinical trials, and may possibly serve as a substitute for the latter in determining therapeutic efficiency.

AUTHORS' SUMMARY.

INCIDENCE OF MASTITIS AND THE INFECTING ORGANISMS IN FOUR DAIRY HERDS.

JOHN G. HARDENBERGH and CARL F. SCHLOTTHAUER, *J. Infect. Dis.* **40**:667, 1927.

The results of the study of sixty-eight cases of mastitis indicate the prevalence of streptococci as infecting agents in the disease, although other organisms, particularly staphylococci and members of the colon-typhoid group, may show occasional periods of predominance. The veterinarian seldom sees cases of bovine mastitis that are not complicated by infection. It is believed that the incidence of the more severe cases of mastitis can be materially reduced in all herds by adherence to a few simple rules of dairy hygiene, such as the isolation of animals with mastitis, the avoidance of disseminating the infection from infected cases, the prevention of dietary disorders and precautions against traumatism.

AUTHORS' SUMMARY.

EXCRETION OF ANTISEPTIC DYES THROUGH THE MAMMARY GLAND. VICTOR BURKE and E. A. RODIER, *J. Infect. Dis.* **40**:673, 1927.

Neutral acriflavine was excreted through the mammary gland of the cow following the intravenous injection of from 7 to 11 mg. per kilogram of body weight. The milk was well colored. The injection of 11 mg. per kilogram caused a severe reaction and a temporary cessation of the milk flow. Although the experiments failed to demonstrate an increase in the bacteriostatic action of the milk following the intravenous injection of neutral acriflavine, there is reason for believing that injection of the dye may affect the organism in the udder.

The intravenous injection of gentian violet caused more severe reactions than acriflavine and mercurochrome-220 soluble caused still more severe and prolonged symptoms. Apparently, these dyes were not excreted by the mammary gland.

AUTHORS' SUMMARY.

THE BACTERIOLOGY AND CHEMISTRY OF ADULT DUODENAL CONTENTS. ARTHUR ISAAC KENDALL, ALEXANDER ALFRED DAY, ARTHUR WILLIAM WALKER and RERA CORDELIA HANER, *J. Infect. Dis.* **40**:677, 1927.

The results of the chemical and bacteriologic study of fifty specimens of duodenal contents obtained from a consecutive series of adults, recorded herewith, afford some substantiation for each of the prevailing theories of the microbic content of this part of the alimentary tract. Approximately one half of the specimens obtained failed to yield significant numbers of microorganisms in artificial cultural mediums; the remainder varied from moderate cultivations, yielding bacteria that were nearly inert chemically except for the production of acid, to heavy growths, reminiscent of those that would have confidently been anticipated had the specimens come from the lower levels of the small intestine.

Direct evidence of a microbicidal action of the duodenum or its contents was not detected, though many specimens failed to show bacteria, even on direct microscopic examination. This does not, however, in itself, preclude this possibility, although the positive evidence deduced from the readiness with which many duodenal specimens yielded viable organisms is rather against it.

The relative abundance of members of the mucous-capsulatus group, of the enterococcus and of staphylococci in the specimens studied suggests that these organisms are rather easily adaptive to the duodenal environment of the adult.

The occurrence of gas bacilli in three of the duodenal specimens indicates that this organism is to be regarded as a potential resident of the duodenum.

The number of cases is far too small to permit generalization, but it is surmised that one essential condition for an exuberant growth of gas bacilli is a low acid content in the duodenum. In the cases cited, the low acidity was due both to a paucity of cultivable lactic acid producing bacteria and to an overgrowth of alkali producing microbes. Further study of such cases is much needed.

AUTHORS' SUMMARY.

TYPES OF HEMOLYTIC STREPTOCOCCI IN CERTIFIED MILK. WILLIAM D. FROST, MILDRED GUMM and ROBERT C. THOMAS, J. Infect. Dis. 40:698, 1927.

The milk from about 1,000 cows on five different certified farms has been plated on blood agar about once a month throughout the period of one and one-half years.

The samples were from groups of ten cows. Hemolytic streptococci of the true beta type appeared in 28.6 per cent of the samples. The number of such streptococci in the samples was usually small: in 65 per cent, less than 1,000 per cubic centimeter, and in 94 per cent, less than 10,000 per cubic centimeter.

Classification of 394 cultures of the true beta type, by means of seven different tests, placed them in six different species. Five of these, the mastitidis, infrequens, subacidus, hemolyticus I and epidemicus have been described before. One new species is described, *Streptococcus asalignus*.

All of the identified streptococci found in certified milk are of the bovine type with the exception of four cultures which proved to be *Streptococcus epidemicus* Davis.

The method of procedure used in this work for examining milk and identifying streptococci promises to be of distinct value in the production of milk of the highest quality.

AUTHORS' SUMMARY.

PERIODIC EXAMINATION OF THE STREPTOCOCCI OF THE HUMAN THROAT. C. IRIS FOX and DORIS M. STONE, J. Path. & Bact. 30:377, 1927.

Periodic examination of the throats of six persons were made over a period of time. Seven hundred and seventy-five colonies were isolated from the inoculated plates and cultured in the various sugars used in the Holman classification. It is concluded that the streptococcal content of the human throat maintains a constant standard as regards both quantity and type; the only important change associated with local pathologic conditions is invasion by hemolytic streptococci.

E. E. M. HALL.

AMEBIC CHOLECYSTITIS. J. TRALAUD, Médecine 8:197, 1926.

Living amebas were found in the bile in cases of cholecystitis. Amebic cholecystitis may occur in dysentery owing to invasion from the intestine or by the blood stream.

THE TRANSMISSION OF LEPROSY TO THE INFERIOR MONKEYS. A. H. ROFFO, Bol. Inst. Med. Exper. 4:64, 1927.

In inferior monkeys inoculated with organisms from human leprosy, clinically and histologically typical lepromas developed containing acid-fast organisms. The incubation period varied from thirty to thirty-five days with the height of development at sixty days. Reinoculation of three monkeys, four months after the first reaction to inoculation, produced new lepromas within a period of fifteen days. In neither instance was any systemic reaction noted. The receptivity of the monkey varied with different races.

INVASION OF *STRONGYLOIDES INTESTINALIS* INTO THE UROGENITAL TRACT. WALTER ROBITSCHKE, *Centralbl. f. Bakteriologie*. **101**:419, 1927.

Robitschke reports finding *Strongyloides intestinalis* in the urine of a woman with frequent and burning urination. Repeated search for worms in the stools failed to reveal any.

PAUL R. CANNON.

THE LOCAL TISSUE REACTIONS OF BACTERIA. H. DOLD, *Centralbl. f. Bakteriologie*. **102**:1, 1927.

Dold has tested the necrotic effects of the intracutaneous injection of various aerobic bacteria. His procedure is to suspend about 5,000,000 organisms in 1 cm. of salt solution and to inject this into the skin of pigment-poor, previously depilated guinea-pigs and rabbits. Three plates show the effects at the end of one day and of four days. Influenza bacilli, pneumococci, gonococci and meningococci exerted only a small effect; among the streptococci, most strains resembled the pneumococcus, but in some instances there was a marked inflammatory reaction. The staphylococci could be divided into toxic and nontoxic strains by the reaction. All the typhoid strains were markedly necrotizing, the paratyphoid more so. It is believed that this method offers a useful supplement to the ordinary bacteriologic methods of diagnosis.

PAUL R. CANNON.

THE PATHOLOGIC CHANGES IN THE DIENCEPHALON IN RABIES. B. S. SLOTWER, *Virchows Arch. f. path. Anat.* **261**:787, 1926.

Inflammatory and degenerative changes were found in the diencephalon. The infiltration was composed of glia cells and lymphocytes; the latter were about the vessels, either diffuse or in nodules. Many ganglion cells were degenerated.

ROY GRINKER.

THE PRECIPITATION OF BACTERIA BY DYES. HANS RUBINSTEIN and FRANZ WINDHOLZ, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:102, 1926.

The authors have tested various dyes as to their effects in inducing the precipitation of various bacterial suspensions. The results are expressed as the precipitation titer, that is, the highest dilution of dye causing precipitation. In dyes of the same group, the precipitating effect varied directly with the presence of free amino groups; basic dyes always showed a positive precipitation titer; the transformation of a basic dye to an acid dye raised the precipitation titer. Gram-positive bacteria flocculate in general at a higher precipitation titer than do the gram-negative bacteria.

PAUL R. CANNON.

A NEW METHOD FOR THE DEMONSTRATION OF THE LYTIC BACTERIOPHAGE. WALDEMAR GOHS, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:139, 1926.

Gohs' method consists in streaking an agar slant with an appropriate culture and adding the lytic bacteriophage in a given dilution to the bottom of the test tube. The culture is then incubated for twenty-four hours. At the end of this time there is a clear zone from 1 to 3 cm. in length, in which growth is sparse or absent. Above this is a normal growth. The advantages of the method are discussed.

PAUL R. CANNON.

THE LYSOZYM. LUDWIG SURÁNYI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:166, 1926.

Surányi reports studies on the lytic enzyme originally described by Flemming in 1922. The effects of this enzyme on solutions of egg-white and cultures of a

sarcina are reported. The enzyme is resistant to light, loses its activity after exposure for one hour at 100 C., is practically without effect in concentrations under 1:80 and, in general, resembles the properties of the bacteriophage.

PAUL R. CANNON.

THE PROVOCATION RECURRENCE, SUPERINFECTION AND REINFECTION IN RECURRENT FEVER. J. L. KRITSCHESKI and A. M. BRUSSIN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:180, 1926.

The authors show that second infection of an animal can call forth the appearance of spirilla from the first infection, thus indicating that Ehrlich and Hata's method of determining sterility in experimental recurrent fever is incorrect. Superinfection in recurrent fever can also be secured.

PAUL R. CANNON.

ANTHRAX. E. SINGER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:284, 1926.

Singer describes studies of the changes due to anthrax infection by subcutaneous inoculation. The principal metastases are in the spleen and lymph nodes in which the organisms are phagocytized to a marked degree. Histologically, the most marked general changes are seen in the liver, in a pronounced fatty degeneration and diminution in glycogen.

PAUL R. CANNON.

BACTERIAL MUTATION AS EFFECTED BY DISINFECTANTS. FRIEDRICH HODER and KIYOSHI SUZUKI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:361, 1926.

The authors claim that the cultivation of members of the colon-typhoid group in agar and broth containing phenol, mercuric chloride and chloramine causes changes in the organisms similar to those which occur in spontaneous mutation or as the result of a bacteriophage. The antigenic properties were also affected.

PAUL R. CANNON.

THE ADSORPTION OF THE LYTIC BACTERIOPHAGE BY BACTERIA. WALDEMAR GOHS and IRENE JACOBSON, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:412, 1926.

The authors find that the b-lysin is bound by the homologous as well as the heterologous bacteria, the homologous bacteria binding the lysin much more strongly. The adsorption of the lytic bacteriophage is only in part irreversible. The resistant nonlysogenic homolyogous bacteria adsorb the lysin as strongly as the lytic-sensitive bacteria. They conclude that the binding of the lytic bacteriophage by the homologous bacteria is the result of physicochemical forces.

PAUL R. CANNON.

THE THERMORESISTANCE OF BACTERIA AND ITS SIGNIFICANCE IN AUTOLYSIS. WALDEMAR GOHS and IRENE JACOBSON, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:441, 1926.

Certain strains of Shiga-Kruse dysentery bacilli have a high resistance to heat, namely, from 57 to 75 C., for one hour. This property may be the result of a decrease in coagulability, the consequence of abnormal activity of digestive ferments.

PAUL R. CANNON.

DIFFERENTIATION OF ENTEROCOCCI. N. Kovács, Ztschr. f. Immunitätsforsch. u. exper. Therap. **49**:450, 1926.

Kovács discusses the significance of the enterococcus and the importance of differentiating it from *Streptococcus viridans*. He finds that the best differentiating medium is a blood agar plate of dextrose, on which the enterococcus produces a gray color.

PAUL R. CANNON.

DIFFERENTIATION OF PARACHOLERA STRAINS FROM TRUE CHOLERA VIBRIOS. N. Kovács, Ztschr. f. Immunitätsforsch. u. exper. Therap. **49**:457, 1926.

A strain of organisms resembling the cholera vibrios was isolated from the intestinal contents at autopsy on persons who had not shown symptoms of cholera; this strain was first found at the El Tor quarantine station by F. Gotschlich and is known as the El Tor strain. The author reports cultural studies of this El Tor strain and strains of true cholera vibrios, using both blood agar and culture plates and Voges plates in which the hemoglobin had been transformed into methemoglobin. The true cholera vibrios have a lytic action on the usual blood agar medium. They have a similar action on the Voges medium. The El Tor strain causes changes in the usual blood agar medium, which differ somewhat from that caused by the cholera vibrios, but in the Voges medium change is not noted.

PAUL R. CANNON.

A NEW THEORY OF BACTERIOPHAGE ACTION. W. GOHS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **49**:532, 1927.

The action of enterokinase and that of lysokinase (or the bacteriophage lysin) showed a marked similarity. The enterokinase acts as an activator of the tryptic ferment of the pancreas; it originates in definite products of the splitting up of the proteins of the substratum; it may be presumed that in an analogous way certain products of the splitting up of the bacterial plasma act as bacteriophage. Enterokinase and bacteriophage act analogously. They aid the access of the ferment to the sensitive constituents of the substratum and thus increase the activity of the ferment.

PAUL R. CANNON.

THE TUBERCULOUS PRIMARY COMPLEX IN THE LIVER. M. NORDMANN, Ztschr. f. Tuberk. **47**:193, 1927.

In an infant, aged 113 days, the autopsy revealed a generalized nodular tuberculosis of almost all the organs with the exception of the brain and the meninges. The largest nodule, fully caseated, was found in the right lobe of the liver. The regional lymph glands were the largest in the whole body, and they were completely caseated. The hepatic focus contained large numbers of tubercle bacilli, and its marginal zone contained some new formed connective tissue. All the other foci did not show a fibrous reaction. Since an active pulmonary tuberculosis was found in the mother, the author concludes that the portal of entry in this case was the placental blood, and that the first implantation of bacilli occurred in the liver, giving rise to the development of a typical primary complex.

MAX PINNER.

A NEW METHOD FOR THE CULTIVATION OF ANAEROBIC BACILLI. SEIGO HOSOYA, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) **4**:103, 1925.

Pure crystals of L-cysteine hydrochloride were prepared from horse hair by reduction for about twenty-four hours with hydrochloric acid and tin leaves (Baumann's method); removal of the tin by hydrogen sulphide, evaporation in vacuo at from 40 to 50 C., and recrystallization of the white, needle-like crystals thus formed, from a solution in absolute alcohol.

The addition of cysteine to broth produces an absolutely anaerobic condition in the depth of the fluid even when precaution is not taken to exclude air: 0.001 per cent *l*-cysteine hydrochloride, p_H from 7.2 to 7.4, allows rapid growth of anaerobic bacilli without petrolatum seal, favors production of toxin by *Bacillus tetani* and allows the formation of the spores. Substitution of *l*-cystine, taurine and thioglycolic acid in broth containing dextrose did not allow growth of the organisms aerobically. The *l*-cysteine reduces methylene blue at room temperature and takes up molecular oxygen immediately in slightly alkaline medium.

ELECTRIC SOLUTION TENSION OF METALS AND THEIR DISINFECTIVE ACTION. MASAHIKO KUROYA, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) 4:107, 1925.

When powdered metal with a higher solution tension (magnesium and zinc, for example) is added to a solution of salt of a metal with lower solution tension (for example, $CuCl_2$) the former metal drives the latter from solution, and the bactericidal and agglutinating power of the salt solution, for typhoid and coli bacilli, is at the moment greatly increased. The direct relationship between stimulation of salt agglutination and the toxicity for bacteria is, however, doubtful since with staphylococci the simple solution of $CuCl_2$ is more bactericidal than the solution plus zinc or powdered magnesium, and certain solutions such as $CuCl_2$, $AlCl_3$ and $Pb(NO_3)_2$, even when diluted, were highly agglutinative for typhoid organisms but failed to kill them during so short a period.

THE INFLUENCE OF THE SULPHUR-CONTAINING SUBSTANCES ON THE GROWTH OF ANAEROBIC BACILLI. SEIGO HOSOYA and SHIGEKI KISHINO, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) 4:123, 1925.

Various kinds of anaerobic micro-organisms fail to grow in a medium containing a tryptic digest of gelatin (which contains the least amount of cystine) as the source of nitrogen, even with added dextrose and sodium formate. With the addition of cystine or of a Na_2S , however, growth anaerobically was profuse; and with either cysteine or H_2S , growth resulted even without the exclusion of air. The addition of S, SO_4Na_2 , $NaHSO_4$, Na_2SO_3 , $Na_2S_2O_3$, *l*-tryptophane, *l*-tyrosine, taurine or Na-taurocholate did not suffice for growth. It is possible that anaerobic bacilli need the SH group for the synthesis of their own proteins, that for growth they need the energy released in the production of H_2S from sulphur-containing substances, or that H_2S generated from the effective S compounds gives its labile hydrogen to an auto-oxidizable substance of the bacilli which enables them to grow. Many aerobic organisms lack cystine in their body proteins; so if anaerobic organisms should contain more cystine than the aerobes, it would be of interest.

THE REDUCTION OF L-CYSTINE BY BACILLUS COLI. SEIGO HOSOYA and HIDETAKE YAOI, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) 4:141, 1925.

Bacillus coli communis grown in a protein-free synthetic medium containing *l*-cystine produces cysteine, which according to Okuda's iodine method of determination increases daily to an optimum concentration after the fifteenth or the twentieth day, and is more abundant in anaerobic cultures.

THE CYSTINE CONTENT OF PEPTONES FOR BACTERIOLOGIC USE. HIDETAKI YAOI, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) 4:145, 1925.

Analyses of eleven commercial preparations of peptone by Okuda's iodine method revealed that the cystine content varied from 0.807 to 0.04 per cent. Three preparations of gelatin were also tested and found to contain traces of cystine (from 0.01 to 0.022 per cent), a fact often overlooked.

EXPERIMENTAL STUDIES ON A FILTRABLE MICRO-ORGANISM ISOLATED FROM INFLUENZA CASES. M. NISHIBE and H. NAKAJIMA, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) 4:149, 1925.

A filtrable obligatory anaerobic micro-organism which morphologically and culturally was like *Bacterium pneumosintes* (Olitsky and Gates) was isolated in pure cultures in the Smith-Noguchi ascites-kidney medium from the filtrates of nasopharyngeal washings in three early cases of influenza and from a filtrate of the emulsified lung in a case of influenzal pneumonia. Fifteen rabbits inoculated intratracheally with cultures, or with the filtrate of an emulsion of the lung of an inoculated animal, underwent only slight changes in temperature or in the number of mononuclear leukocytes in the blood, and had only small hemorrhages in the lungs and no bronchitis; hence, the pathogenicity of the organism for rabbits is as yet undecided.

MICROSCOPIC CHANGES OF EXPERIMENTAL EPIDEMIC ENCEPHALITIS IN RABBITS, WITH NOTES ON SPONTANEOUS ENCEPHALITIS IN RABBITS. MASUJIRO NISHIBE, Sc. Rep. Gov. Inst. Infect. Dis. (Tokyo Imperial University) 4:223, 1925.

The virus of epidemic encephalitis which prevailed in the summer of 1924 in Japan, is pathogenic for rabbits, polio-encephalotropic, filtrable and transmissible to series of rabbits.

Microscopic changes in experimental epidemic encephalitis in rabbits consist of marked degeneration of ganglion cells with prominent vacuolization. Other changes include remarkable neuronophagy, regressive changes of glial cells, hyperemia and hemorrhages. These lesions are distributed for the most part in the gray matter in the following order: (1) thalamus and midbrain, (2) pons, medulla oblongata and cerebellum, (3) spinal cord and cerebral cortex and (4) hippocampus. Nucleus caudatus and lentiformis are free from degeneration of ganglion cells and neuronophagy except for a slight hyperemia and small hemorrhages. The leptomeninges show hyperemia and small hemorrhages.

A spontaneous encephalitis was noticed in apparently healthy Japanese rabbits. The meningeal and perivascular round cell infiltration and proliferation of glial cells in experimental epidemic and herpetic encephalitis in rabbits reported by previous workers are, in my opinion, nothing but spontaneous lesions of rabbits.

AUTHOR'S SUMMARY.

SURGICAL ASPECTS OF ASCARIS LUMBRICOIDES. A. I. LUDLOW, China M. J. 41:134, 1927.

Ascaris lumbricoides is one of the most common parasites in Korea. Of 5,000 examinations *Ascaris* was present in 53.2 per cent; of a second series of 4,000 examinations, it was present in 44.2 per cent. Of 454 surgical patients, 207 were infested with *Ascaris*. Three cases of appendicitis, two of abscess in the abdominal wall with perforation at the umbilicus, all in children, and one case of *Ascaris* in a gallstone have been observed. The following conditions due to *Ascaris* are reported: (a) intestinal obstruction, gangrene of a portion of the ileum; (b) intraperitoneal abscess, postoperative appearance of *Ascaris* through the drainage incision; (c) general peritonitis from perforation of the ileum.

Immunology

INFLUENCE OF ACID GROUPS ON SEROLOGICAL SPECIFICITY OF AZOPROTEINS. K.

LANDSTEINER and J. VAN DER SCHEER, J. Exper. Med. **45**:1045, 1927.

Azoproteins from nonacid azo-compounds were prepared and studied serologically. Substituents like CH_3 , OCH_3 , NO_2 , Cl, Br, I in the aromatic nucleus altered the reactions only moderately, but acetyl-para-phenylenediamine and para-amino-acetophenone had a marked effect on the specificity of the compound protein. Antigens from acid compounds have distinctive characteristics; the acid radicals suspend the reactivity with immune serum for nonacid antigens, and serums against acid antigens react only feebly with nonacid azoproteins.

INFECTIVITY OF TYPE III PNEUMOCOCCUS FOR RABBITS. WILLIAM S. TILLET,

J. Exper. Med. **45**:1093, 1927.

Of eleven strains from human sources, ten were slightly virulent for rabbits, although they were capsulated and highly virulent for mice. One strain became highly virulent for rabbits. The bacteremia in rabbits produced by type III pneumococci differs from that produced by nonencapsulated R forms of pneumococci; hence, the mechanism of resistance cannot be the same. Nonencapsulated R forms are ingested by the leukocytes in the circulating blood, while type III pneumococci are not.

RELATION OF ANAPHYLAXIS TO IMMUNITY. W. H. MANWARING, H. D. MARINO,

T. C. McCLEAVE and T. H. BOONE, J. Immunol. **13**:319 and 357, 1927.

The main outcome of the experiments here recorded is that apparently marked chemical changes take place in antigens on injection into the animal body. The view is supported that many immunologic reactions depend on the formation of denaturalized products which as secondary antigens. These may be antigen-antibody reactions that cannot be demonstrated by current immunologic methods.

REACTIONS IN HAY-FEVER. LOUIS B. BALDWIN, J. Immunol. **13**:345, 1927.

Extensive skin tests were made in persons with "direct inheritance of hay-fever," but who were not suffering from any form of hypersensitiveness. One person gave a skin reaction without other evidences of hypersensitiveness; five persons developed skin reactions and also hay-fever while under observation.

THE BLOOD CLOT METHOD OF IMMUNIZATION. JOHN F. ANDERSON and GEO. F.

LEONARD, J. Immunol. **13**:365, 1927.

In the immunizing of horses in large numbers with certain bacteria and their products, the advantages of the blood clot method outweigh its disadvantages.

ANTIGENIC PROPERTIES AND VIRULENCE OF MAMMALIAN TUBERCLE BACILLI.

STUART MUDD and JACOB FÜRTH, J. Immunol. **13**:369, 1927.

Virulence and the antigenic properties tested may vary independently.

THE RELAXATION OF HISTAMINE CONTRACTIONS IN SMOOTH MUSCLE BY CERTAIN

ALDEHYDES. ARTHUR ISAAC KENDALL, J. Infect. Dis. **40**:689, 1927.

The relaxation, by certain aldehydes, of contractures induced in the intestines and uterus of guinea-pigs by histamine, and certain histamine like substances, has been demonstrated graphically by kymograph tracings. This reaction is not due exclusively to the aldehyde group, per se, but is markedly influenced by the composition and structure of the aldehyde molecule as a whole.

The absence of oxygen on the carbon atom next the aldehyde group appears to predispose the aldehyde molecule as a whole toward reactivity. The presence of oxygen on the carbon atom next the aldehyde group restrains, or prevents, the reactivity of the aldehyde radical.

It must be emphasized that the evidence of aldehyde activity presented herewith is based solely on physiologic response induced in smooth muscle. It does not necessarily follow that these reactions would take place quantitatively in the test tube, although chemical literature contains many instances in which such aldehyde-amine reactions have been investigated.

The method lends itself to the detection of free histamine and histamine-like substances. Many of these products found in peptones, proteoses, tissue extracts, blood, urine and hormones, exert a depressor action on blood pressure, but fail to induce contracture in the guinea-pig intestine.

Finally, it must be distinctly recognized that substances other than amines cause contracture in the intestines of guinea-pigs, and it is equally certain that substances other than aldehydes, for example, epinephrine hydrochloride, relax these contractures.

THE PRECIPITIN REACTION OF FIBRINOGEN. LUDVIG HEKTOEN and WILLIAM H. WELKER, *J. Infect. Dis.* **40**:706, 1927.

The fibrinogens of beef, dog, horse, human, sheep and swine blood are precipitinogenic. These fibrinogens, to which may be added those of the goat, guinea-pig, rabbit and rat, have antigenic elements of properties that are more or less common. Consequently, fibrinogen is not necessarily wholly different for each of these species, as seems to be the case with serum proteins and hemoglobin, but to a varying extent the same, resembling in this respect casein, lens proteins and thyroglobulin; and the principle of specificity for species does not seem to hold fully in the precipitin reaction of mammalian fibrinogen, but the possibility that there may be species-specific elements in fibrinogen, as prepared ordinarily, is not excluded. While the mammalian fibrinogens just enumerated are not strictly species-specific, there appears to be also some relationship between them and chicken fibrinogen so far as indicated by the precipitin reactions that have been observed. This fact suggests that mammalian and bird fibrinogens are not wholly distinct and different. The fibrinogens of the chicken, duck, goose, guinea-hen, pigeon and turkey appear to have in large measure common precipitinogenic properties. Taken together, the results of the precipitin reactions of fibrinogen accord well with the fact that fibrinogen, a normal globulin of the circulating blood, is sufficiently uniform throughout the animal kingdom to give a characteristic fibrin gel with pig's thrombin. Finally, it seems probable that as it is possible to obtain precipitin serum that is practically specific for blood fibrinogen, the precipitin test may be of value in efforts to trace the origin of fibrinogen and its relation to other substances.

BLOOD GROUPING OF BRAZILIANS. J. ABEN-ATHAR, *Sciencia méd.* **5**:145, 1927.

In a miscellaneous series of 274 Brazilians, 50 per cent belonged to group A; 29.5 per cent to group A; 17.8 per cent to group B and 2.5 per cent to group A B. The biochemical index, i. e., the ratio between groups A and B, was 1.6. Among eighty-four white Brazilians, the proportions represented by the different groups were respectively, 42.8, 40.4, 14.2 and 2.3 per cent; among forty-six Portuguese, 34.7, 47.8, 13.0 and 4.3 per cent; among ninety-three half-breeds, 51.6, 31.1, 15.0 and 2.1 per cent; among seventy-two mulattoes, 44.4, 33.3, 19.4 and 2.7 per cent; among sixty-five half-breed Indians, 61.5, 15.3, 21.5

and 1.5 per cent, and among thirty-two negroes, 40.6, 25.0, 28.1 and 6.2 per cent, respectively. The negroes and half-breeds have for some time shown a progressive decrease in Brazil.

EXPERIMENTAL SYPHILIS. P. MANTEUFEL and W. WORMS, *Centralbl. f. Bakt.* **102**:23, 1927.

After the spontaneous healing of syphilis in the rabbit there is a certain immunity to a second infection. This resistance persists even after any latent infection of the lymph gland has been cured by neoarsphenamine or other therapeutic reagents. The protection against a second infection, consequently, is not due to latent syphilis of the gland. Also, since it appears possible completely to eliminate spirochetes in rabbits with syphilis by therapeutic measures, doubt is cast on the validity of Neisser's dictum that acquired immunity against a second infection only means the persistence of an existing first infection. Immunity to a second infection with a homologous strain in rabbits with syphilis is due not solely to the "chancre immunity," but also to the infection of the lymph gland.

PAUL R. CANNON.

SEROLOGIC TEST FOR BLOOD GROUP O. F. SCHIFF, *Klin. Wchnschr.* **6**:303, 1927.

Schiff failed to obtain any specific agglutinins against corpuscles of group O by immunizing rabbits. After removing by absorption the normal agglutinins in beef serum for the corpuscles of groups A and B, he found that in some cases a strictly specific agglutinin for group O corpuscles was present in the treated beef serum. This result shows that corpuscles in group O contain a special antigenic substance.

NOMENCLATURE OF BLOOD GROUPS. F. VERZÁR, *Klin. Wchnschr.* **6**:347, 1927.

The use of letters O, A, B and AB in place of numbers is urged, in order to stop the confusion due to the interchange of Jansky's groups I and IV in Moss' system.

THE RELATIONSHIP OF LIPOID IMMUNIZATION TO THE STIMULATING ACTION OF TAR. PIETRO RONDONI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:91, 1926.

Rondoni injected rabbits with alcoholic extracts of various organs, mixed with swine serum. Then the ears of these immunized animals were painted with tar at weekly intervals. Other animals were injected with swine serum alone, while others received only alcoholic organ extracts. The results are only suggestive, due to a high fatality rate, but Rondoni feels that the injection of the lipid serum mixture and also of a serum alone exerted a marked restraining influence on epithelial proliferation due to the tar stimulation. He suggests that sensitization to the foreign protein may be a factor in restraining epithelial growth.

PAUL R. CANNON.

HEMAGGLUTINATION IN ANIMALS AND IN MAN. LUDWIG FLEISCHER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:121, 1926.

The hemagglutinins in human and animal serums are compared in their reactions. Tables are given showing the interrelationships.

PAUL R. CANNON.

AN ATTEMPT TO DEMONSTRATE LIPOIDS BY A BIOLOGIC REACTION. L. G. PERETZ, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:146, 1926.

The author uses the combining power of saponin for lipoids to test the hemolysis of cells after adding saponin to lipid extracts, serums, etc. By

this method he finds that the lipoid content of various serums varies greatly. In strongly positive Wassermann serums he finds the lipoid content quite low, whereas it is high in pregnancy. He discusses the applicability of this method to various biologic problems.

PAUL R. CANNON.

VACCINATION AGAINST TUBERCULOSIS. VINCENZO BISCEGLIE and ALEXANDER JULHÁSZ-SCHAFER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:251, 1926.

The authors discuss at length the problem of immunity to tuberculosis, reviewing in considerable detail the literature. They conclude that immunity to tuberculosis is fundamentally of a histogenic character rather than due to humoral antibodies directly, and that it is primarily the result of allergy. The best results to date in vaccination have been obtained with living avirulent organisms, and the great problem is to determine means of reducing the virulence of the tubercle bacilli so that they can be used with safety.

PAUL R. CANNON.

VACCINATION AGAINST TUBERCULOSIS BY INOCULATION WITH LIVING ORGANISMS. VINCENZO BISCEGLIE, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:272, 1926.

The author diminished the virulence of tubercle bacilli by exposing them to radium emanation, and noted a change in the structure and staining reactions at the same time. Radiation appeared to destroy the virulence without interfering with the vaccinating powers. Guinea-pigs injected with these strains developed tubercles, and became hypersensitive and markedly immune to the subsequent injection of virulent tubercle bacilli.

PAUL R. CANNON.

CONTRIBUTION TO THE STUDY OF THE ANTIGEN ACTION OF BACTERIAL LIPOIDS. S. ZURUKZOGU, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:304, 1926.

From cultures of *Bacillus typhosus*, the lipoids were extracted by drying of the original substance to constant weight and subsequent treatment with ether, benzol and acetone, as well as alcohol. Before the extraction was made, the original material was tested as to its antigenic activity. High agglutination titers were obtained in guinea-pigs. No definite antigenic action of the bacterial lipoids obtained by this method could be demonstrated. This was true primarily of the ether, acetone and alcohol extracts, which even in large quantities, either alone or mixed with foreign protein, did not cause any significant antibody formation in guinea-pigs. The injection of guinea-pigs with benzol extracts, alone or in combination with swine serum, gave a somewhat more definite reaction. The agglutination titer in these cases was even higher, but the agglutination itself was incomplete, finely flocculated and without any gradation corresponding to serum dilution. The addition of foreign protein components (swine-serum) did not show any accelerating action as in organic lipoids. Neither was any inhibition observed as described by Mera-Kovacs-Kraus; the agglutinin titer was neither higher nor lower than that observed in the extract alone. Cross experiments, on the one hand with ether, benzol, acetone and alcohol extracts and a horse kidney-extract antiserum, and on the other hand with ether, benzol, acetone and alcohol extract antiserum and a horse kidney-extract, were completely negative. The lipoids of the typhoid bacillus would thus seem not to be related to the lipoids of cells and organs, as regards antigenic powers. The antigenic action of the typhoid bacillus depends on its protein rather than on its lipoid content.

PAUL R. CANNON.

ANAPHYLAXIS IN FROGS. K. A. FRIEDE and M. K. EBERT, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:329, 1926.

Active and passive anaphylaxis to erythrocytes and foreign proteins was obtained. In many cases the anaphylactic shock was fatal. The authors were unable to demonstrate antibodies in the blood of the sensitized frogs.

PAUL R. CANNON.

ALLERGY IN LEPROSY. P. BARGEHR, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:346, 1926.

Bargehr reports that he has obtained allergic reactions to material prepared by boiling macerated leprosy nodules. The reactions in general resemble the Pirquet reaction in tuberculosis.

PAUL R. CANNON.

THE MECHANISM OF IMMUNITY TO TYPHOID FEVER. W. JELIN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:354, 1926.

Jelin finds that when an antityphoid bacteriolytic serum of high titer is injected intravenously into rabbits, followed at various intervals by the injection of live typhoid bacilli, that the organisms disappear rapidly from the blood stream. Coincidentally, if a large suspension of bacilli is injected, the animals die, owing, he concludes, to the liberation of endotoxin. The previous injection of 25 cc. of 5 per cent India ink does not influence the reaction. When the bacteriolytic serum is injected a few hours after the typhoid bacilli have been injected, there is not any immediate toxic effect, as the organisms then have all been phagocytized by the reticulo-endothelial cells. Under these conditions, the animals do not act any differently from the controls.

PAUL R. CANNON.

LEUKOCYTIC IMMUNE SERUMS. W. SPÄT and F. HODER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:382, 1926.

Rabbits injected with leukocyte suspensions from guinea-pigs gave a serum that caused agglutination and lysis of the leukocytes of guinea-pigs as well as of cell suspensions of various organs of the guinea-pig. It contained complement fixing bodies also, but did not alter the bactericidal action of the leukocytes.

PAUL R. CANNON.

THE THEORY OF CHEMORECEPTORS: III. THE INHIBITORY ACTION OF PARAFUCHSIN TOWARD ANTIMONY POTASSIUM TARTRATE. R. SCHNITZER and W. SILBERSTEIN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:387, 1926.

In experiments on animals infected with parafuchsin-fast strains of trypanosomes, the trypanocidal action of antimony potassium tartrate was inhibited by preliminary injections of parafuchsin in only about 40 per cent of the cases; the maximum tolerated dose of parafuchsin was necessary to obtain this inhibitory action, and the interval between the two injections was from four to six hours. If normal strains of trypanosomes, i. e., not parafuchsin-fast, are used, the inhibitory action of parafuchsin on the trypanocidal action of antimony potassium tartrate is still less marked. From these observations, the authors conclude that the complex chemoreceptor contains apparently independent specifically sensitive toxin-fixing groups for antimony compounds; in addition to the chemoreceptor system previously described (parafuchsin system), there are still systems the relations of which to each other must be more closely analyzed.

PAUL R. CANNON.

THE THEORY OF CHEMORECEPTORS: IV. COMPARISON OF THE INTERFERENCE PHENOMENON ON NORMAL AND PARAFUCHSIN-FAST STRAINS. R. SCHNITZER and E. ROSENBERG, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:393, 1926.

The authors report experiments in which it was found that in infections with normal strains of trypanosomes, the inhibitory effect of parafuchsin on the trypanocidal action of the acriflavine, sodium acetyl arsenilate and arspenamine is essentially the same for all three drugs; the optimum parafuchsin concentration to obtain this effect is 1:2,000. With parafuchsin-fast strains, the concentrations of which parafuchsin exerts an inhibitory effect on the trypanocidal action of these drugs show a wider range; with these strains the inhibitory effect is evident at concentrations of 1:5,000 to 1:10,000. Parafuchsin-fastness, therefore, exercises a profound influence on the complex chemoreceptor system.

PAUL R. CANNON.

THE ANAPHYLACTIC ANTIBODY AND ITS RELATIONSHIP TO PROTEINS. R. OTTO and O. ORNSTEIN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:399, 1926.

The authors discuss the conflicting results of Doerr and Hallauer relative to the fractions of protein in which the antibodies are present.

PAUL R. CANNON.

THE SEROLOGY OF CEREBROSPINAL FLUID: III. HEMAGGLUTININS. G. D. ARONOWITSCH, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:406, 1926.

The previous observations of Kafka relative to the presence of hemagglutinins for sheep erythrocytes in cerebrospinal fluid are confirmed. The phenomenon is not due to the presence of globulins in the fluid.

PAUL R. CANNON.

THE LINKAGE RELATIONS OF THE BLOOD GROUPS. LAURENCE H. SNYDER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:464, 1926.

Snyder discusses the claims by certain authors that there is a linkage between the blood groups and some pathologic, anatomic or physiologic condition, and claims that in every case the conclusions are based on insufficient or irrelevant data.

PAUL R. CANNON.

THE DOUBLE RING PHENOMENON WITH REFERENCE TO THE FRIEDBERGER TYPES. T. IKEDA, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:481, 1927.

Ikeda reports an extensive study of the effect of the double ring when specific precipitation occurs. The upper ring is light and persists, whereas the lower ring is heavy, consists of larger floccules and sinks to the bottom. He considers the upper ring to be a finely flocculated heterogenetic precipitate and the lower ring to be isogenetic. The phenomenon of the double ring occurs only with homogenetic antigens and is, therefore, of value in forensic precipitin tests. He thinks that the upper ring is due to a lipoid-antilipoid union, whereas the lower ring is a protein-antiprotein reaction.

PAUL R. CANNON.

THE INTERFERENCE PHENOMENON WITH CERTAIN TRIPHENYLMETHAN DYE STUFFS. R. SCHNITZER and W. SILBERSTEIN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **49**:551, 1927.

Experiments to determine the interference phenomenon with trypanosan, methyl violet and brilliant green against the trypanocidal action of acriflavine,

sodium acetyl arsanilate, arsphenamine and antimony potassium tartrate, showed that of these dyes only methyl violet inhibited the action of the trypanocidal drugs on normal and parafuchsin-fast strains of trypanosomes of the Nagana Prowazek type. Practically no interference was noted with tryparosan. Brilliant green showed only a slight occasional inhibitory action, especially against arsphenamine. It is evident that Ehrlich's theory of the chemoceptor in its simplest form does not explain this interference phenomenon; it can be explained only on the basis of a more complex chemoceptor with several primary fixing units.

PAUL R. CANNON.

TETANOSPASMIN AND TETANOLYSIN. G. C. REYMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:31, 1927.

Reymann used two strains of *Bacillus tetani* in a standard broth and studied the conditions affecting the formation of tetanospasmin and tetanolysin. Berkefeld filtration of broth containing tetanospasmin frequently led to a weakening of the tetanospasmin. The use of an unfiltered culture was satisfactory for the titration of its toxin content except when there was a high spore content. The effects of the hydrogen ion concentration, alkali reserve and amino-N of the medium on the production of tetanus toxin were also studied.

PAUL R. CANNON.

PURE ISOLATION OF AUTOHEMOLYSIN. MUTSUMI NAMBA, Tohoku J. Exper. Med. **8**:614, 1927.

Serum from a patient with attacks of paroxysmal hemoglobinuria hemolyzed his own washed red blood cells in a dilution of 1:32. Cells treated with the serum and the middle piece of complement obtained in the globulin precipitated with carbonic acid gas from diluted (1:4) normal human serum were extracted with a 10 per cent solution of grape sugar (added in the ratio 1:5) for twenty minutes at from 50 to 60 C. Treatment of the extract of sugar solution with ether extraction and dialysis yielded a fluid which was still hemolytic and did not contain any protein, according to a test with sulphosalicylic acid.

E. B. PERRY.

Tumors

OVARIAN LUTEOMA. S. A. WOLFE, Am. J. Obst. & Gynec. **13**:575, 1927.

A bilateral ovarian tumor, larger on the right side, was seen in a virgin, aged 21. The tumor tissue was grayish yellow, and the cells stained faintly, having a coarsely granular cytoplasm. The tumor cells grew diffusely or in alveolar form, with a mosaic arrangement. The perivascular arrangement and suprarenal cortex pattern were lacking. In view of the character of the tissue and of its growth within the ovarian substance, hypernephroma was ruled out, and the tissue was believed to have arisen from the corpus luteum.

A. J. KOBAK.

TRANSFORMATION OF A MALIGNANT PARAVERTEBRAL SYMPATHICOBLASTOMA INTO A BENIGN GANGLIONEUROMA. HARVEY CUSHING and S. BURT WOLBACH, Am. J. Path. **3**:203, 1927.

A paravertebral swelling at the sixth thoracic level occurred in the back of a child, aged 2 years, following trauma. The lesion proved on exploration to be a cellular sympathicoblastoma (sympathetic neuroblastoma) which was mistaken for a time for sarcoma. The tumor had apparently taken its origin from the region of an intervertebral foramen, and had extended into the spinal canal and into the spinal muscles. Apparently, under the influence of Coley's

toxin, the activity of the growth subsided. Ten years later, owing to the persistence of a paraplegia, an exploratory laminectomy was performed. This disclosed the relic of the former growth the cells of which had become completely differentiated into ganglion, capsules and neurilemma cells. Because of the unusual circumstance which permitted a study of the lesion at two remote periods, the case illustrates particularly well what has been pointed out by others—that a sympathetic neuroblastoma may be the precursor of a ganglioneuroma.

AUTHORS' SUMMARY.

ADENOCARCINOMA OF THE UTERUS OF A RABBIT. G. Y. RUSK and NORMAN EPSTEIN, *Am. J. Path.* **3**:235, 1927.

A spontaneous adenocarcinoma of the body of the uterus, with local invasion and extensive metastases, in a rabbit, aged 4½ years, is described.

FURTHER REMARKS ON TUMORS OF THE GLIOMA GROUP. PERCIVAL BAILEY, *Bull. Johns Hopkins Hosp.* **40**:354, 1927.

It seems possible to subdivide the majority of gliomas into groups, each with a characteristic structure; to gain some insight into the reasons for their structural variability, and to attach to each group a certain prognostic significance.

AUTHOR'S CONCLUSIONS.

INCIDENCE OF CANCER IN FILIPINOS. EDWARD B. VEDDER, J. A. M. A. **88**:1627, 1927.

Contrary to the conclusion of Hoffman, the cancer rate for Filipinos is not lower than the cancer rate in the registration area of the United States. The assumption that cancer is preeminently a disease of civilization is untenable. It is concluded also that with improvement in diagnosis and reports cancer rates in all countries may be expected to increase.

PSEUDO-EPITHELIOMATOUS HYPERPLASIA AT MARGIN OF CUTANEOUS ULCERS. CLEVELAND WHITE and FRED D. WEIDMAN, J. A. M. A. **88**:1959, 1927.

The epithelial hyperplasia at margins of cutaneous ulcers may present in microscopic sections the picture of early squamous celled carcinoma. The danger of an erroneous microscopic diagnosis of carcinoma in such cases is pointed out.

BOTELHO'S REACTION FOR CANCER SERUM. M. C. Reinhard and K. S. TUCKER, *J. Cancer Research* **10**:478, 1927.

Serum from fifty patients with cancer and eight persons who were free from cancer in each instance gave a positive Botelho reaction. The precipitate depends on the presence of serum albumin and serum globulin. The serum of five different animals also gave a positive reaction.

INFLUENCE OF OVARECTOMY ON SPONTANEOUS MAMMARY CARCINOMA IN MICE. CARL F. CORI, *J. Exper. Med.* **45**:983, 1927.

Ovariectomy performed from fifteen to twenty-two days after birth prevented spontaneous adenocarcinoma of the breast, while nonbreeding control mice of the same strain showed a tumor incidence of 78.5 per cent. As three of the spayed mice developed sarcoma, the influence of the ovary on carcinoma of the breast appears to be specific. It is concluded that spontaneous mammary carcinoma in mice depends on a hereditary disposition of the organs, which remains latent in the absence of ovarian function.

PAGET'S DISEASE OF THE NIPPLE AND ITS RELATIONSHIPS. ROBERT MUIR, J. Path. & Bact. 30:451, 1927.

Five cases of Paget's disease of the nipple are described with a number of excellent photomicrographs.

E. M. HALL.

CONCERNING THE BEHAVIOR OF PLEURAL METASTASES IN PARANGLIOMAS. BONNAMOUR, DOUBROW and MONTEGUE, Ann. d'nat. path. 4:141, 1927.

The pleural metastases of a paraganglioma are peculiar in that the cells here are much less differentiated than in the primary tumor and also by the absence of blood vessels. Curiously enough, when the same growth metastasizes to the mediastinum, the primary and metastatic lesions are identical. It is possible that the different behavior of the pleural metastases is due to the avascularity of the secondary tumor. The physiologic condition in which the metastasis is found can be compared with a tumor transplant, which as observed by Policard, grows much better when deprived of blood vessels. On the other hand, in instances in which tissue is growing in vitro, that is to say, in the absence of any blood supply, it loses some of its morphologic characteristics. The authors believe that the vascularity of a tumor plays a rôle in its atypical evolution.

B. M. FRIED.

THE LOCALIZATION OF THE GLOMIC TUMORS (ANGIONEUROMYOMA OF P. MASSON). ASSEN PRODANOFF, Ann. d'anat. path. 4:147, 1927.

Prodanoff reports a case of an "angioneuromyoma" of P. Masson which occurred in a man, aged 68. The clinical and microscopic picture of the tumor is in complete accord with those previously reported by Masson. The tumor was localized at the inner surface of the thigh. This is of interest in that it shows that the growth may be found not only underneath the nails, but in any part of the body.

B. M. FRIED.

SUBCUTANEOUS GLOMIC TUMORS OUTSIDE OF THE FINGER (ARTERIAL ANGIO-NEUROMYOMAS). PIERRE MASSON and LOUIS GERY, Ann. d'anat. path. 4: 153, 1927.

In a previous report, Masson has described a peculiar tumor which was characterized by him as a new growth, the size of a pea, situated underneath the nail, and having a bluish color analogous to that of a recent hematoma. The tumor causes an excruciating pain which radiates to adjacent structures, and occasionally leads to sympathetic trophic or circulatory disturbances corresponding to the homologous side of the trunk and even of the face. The tumor originates apparently from organs situated in the way of certain arteriovenous anastomoses.

Masson compared the neoplasm with the organs of Ruffini and labeled it under the name of "glomus neuro-myoma-artériel." A search in the literature revealed that similar new formations have been reported under the name of "endotheliomas," "peritheliomas," etc. Their seat of predilection is the palmar part of the finger and the plantar part of the toes. A striking feature in these formations is the parallelism of their presence to that of the corpuscles of Wagner-Weissner. Never before have they been reported to be present outside of the tactile areas. The present study of Masson and Gery deals with four cases found in different parts of the body. The histology of the tumor is given in detail.

B. M. FRIED.

COMPARATIVE STUDIES OF THE INFLUENCE OF HYDROLYSATES OF VARIOUS ORGANS ON IN VITRO CULTURES OF NORMAL AND NEOPLASTIC TISSUES. A. H. ROFFO, *Bol. d. Inst. de med. exper.* 4:5, 1927.

Hydrolysates of various tissues that were triturated in sulphuric acid solution, 3 per cent, heated, cooled, neutralized and filtered, inhibited the growth of tissue cultures: the hydrolysates of homologous tissue were more inhibitory than those of heterologous tissues; the intensity of toxic effect decreased with different tissues, tumor, embryo, lung and spleen, in the order named, and neoplastic tissue cultures were more affected than normal tissues. Hydrolysates were less inhibitory than autolysates and the possibilities were considered: of the presence of both inhibitory and stimulative substances, of primary effects by the fresh extracts and autolysates on the blood pressure, and of the action not only of a chemical substance but of a lytic enzyme.

THE RELATION OF CHOLESTEROL TO THE GROWTH IN VITRO OF NORMAL AND NEOPLASTIC TISSUES. A. H. ROFFO, *Bol. d. Inst. de med. exper.* 4:55, 1927.

The decrease in the amount of cholesterol in the medium during the growth of tissue cultures is discussed as a probable result of an increased permeability of the cell membranes, which, according to other authors, bears a quantitative relation to the cholesterol content, and favors nutrition and more energetic growth, which in turn would increase the absorption of cholesterol from the medium.

ACTION OF HYDROLYSATES OF ORGANS AND TUMORS ON NEOPLASTIC CELLS. A. H. ROFFO and J. VILLANUEVA, *Bol. d. Inst. de med. exper.* 4:92, 1927.

Hydrolysates of different organs when tested for cytolytic action in vitro affected neoplastic cells more than normal cells and were effective with the cells from heterologous animals, although the hydrolysates of lung, heart, kidney, spleen, liver, brain and suprarenal capsule accomplished about the same amount of cytolysis (69 per cent), while with cells of homologous animals the destruction is more active and varies with the tissue lysate used. The presence of an enzyme specific for each organ is considered probable.

Medicolegal Pathology

RECENT EXPERIENCES WITH FATAL ARSENIC POISONINGS. W. SCHWARZACHER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:257, 1927.

The eastern Alpine people of Graz and less populated parts of Styria employ arsenic for suicidal and homicidal purposes; it is their "house-hold poison." In Vienna, not far to the north, there were only twenty-seven deaths from arsenic during the forty years, from 1883 to 1923, whereas in the last five years seventeen were observed in Graz and eight more in the contiguous country districts; yearly there are about six deaths from arsenic. The article contains nothing new, but from such an unusually rich experience there are naturally highly valuable suggestions for the recognition of arsenic poisoning solely by the observations at postmortem examination. Chief among such tell-tale signs are the hemorrhages in the lining of the left ventricle of the heart and deposits of the yellow trisulphide in the lining of the stomach and bowel where the trioxide has been acted on by hydrogen sulphide. Such yellow precipitates may be found months after death. They disappear when touched with a weak solution of ammonia. This distinguishes them from discolorations caused by bile. Mention is also made of a generalized yellowish color of the stomach

lining encountered in cases of the more chronic poisoning and caused by fatty degeneration. In cases of the more acute poisoning, the stomach lining is red and bestrewn with minute hemorrhages, coalescent in places. In one body such small hemorrhages were found in the ependymal lining of the fourth ventricle of the brain. Grossly visible fatty change of the liver occurs only when the poisoning has lasted for ten days or longer.

E. R. LE COUNT.

NECROSIS IN LYMPHOID TISSUES FROM ARSENIC. R. STRAUMANN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:266, 1927.

This is an account of the experimental production in dogs, rabbits, guinea-pigs and rats of necrosis of the germinal centers of lymphoid tissues caused by arsenic given in a variety of ways and forms. It fails to add much to other reports of such changes made during the past few years.

E. R. LE COUNT.

CHANGES IN THE VEGETATIVE NERVOUS SYSTEM FROM WOOD ALCOHOL. B. MOGILNITZKIE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:302, 1927.

Material was obtained from the bodies of five persons from 20 to 35 years of age, who died from twenty-four to seventy-two hours after poisoning. The ganglions of the spinal cord, sympathetic ganglions of the neck and trunk, retina, nerve plexuses of the heart and alimentary organs, main trunks of nerves, such as the pneumogastric and optic, and important centers of the pons and medulla were studied. The alterations varied somewhat in the different places, but in general were different phases of necrosis and occurred in both ganglion cells and the cells lining their capsules. Necrosis in the latter cells, the satellite cells lining the capsules about the ganglion cells, was noted by van Gehuchten as a characteristic change in rabies.

As a rule, these cells proliferate with most infectious diseases. The degeneration of the retina and optic nerves has been understood for a long time, and has satisfactorily accounted for the blindness and loss of the pupillary action to light caused by methyl alcohol. Mogilnitzkie believes he has equally acceptable explanations for some of the other symptoms of this poisoning. The early pallor replaced by a red skin especially conspicuous on the ears, sweating and dryness of the throat are all connected with necrosis of ganglion cells in vasomotor centers. Abdominal colic and salivation are due to a similar change in nerve centers contiguous to the structures involved, and the association of pallor and tachycardia is especially important, since such symptoms follow experimental stimulation of cervical sympathetic ganglions, in which he also found necrosis of the ganglion cells. He did not perform any experiments on animals with wood alcohol, and, with the exception of investigation of the visual nerve tissues, he has not succeeded in marshalling much support for his contentions from animal experimentation by other investigators. Apparently, studies of these structures in animals poisoned by wood alcohol have not been numerous.

He has some support, however, in the reports of similar alterations produced with ethyl alcohol and chloroform. He fails to describe changes which explain the coma or prolonged drunkenness. It has been known for some time that with this poisoning there is a marked acidosis. Reference has not been made to this. As the molecular weight of the monatomic alcohols increases, so does their toxicity. Amyl alcohol is more poisonous than grain alcohol. Wood alcohol, the lowliest member of the series, is the outstanding exception. During its oxidation, which is incomplete and difficult, formic acid is formed and excreted in the urine with large amounts of lactic and other organic acids. These are,

however, trivial indications of what happens to metabolism in general. A much more comprehensive understanding of the modifications of normal chemical processes is as necessary to account for the symptoms of poisoning by wood alcohol, as is information regarding the morphologic changes.

E. R. LE COUNT.

TRAUMATIC RUPTURE OF THE ESOPHAGUS. A. ESSER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:312, 1927.

One more case of rupture of the esophagus from trauma is added to the six already reported. A common feature is a lengthwise tear at the lower end, usually in the back wall, ascribed to pressure of the content of the stomach up into the esophagus by external violence, and by the food in both pleural cavities, mainly the left. The force is blunt and considerable. In the body Esser examined, 4.5 liters of food were found: 2 in the stomach, 2 in the left pleural cavity, and 0.5 in the right pleural cavity. Death occurred eight hours after the accident, and the margin of the tear had an inflammatory exudate, demonstrated microscopically, a matter of some importance in distinguishing such injuries from the agonal and postmortem defects located in the same region and due to digestion of the wall by gastric juice.

E. R. LE COUNT.

TORN KIDNEY AND INFERIOR VENA CAVA FROM A BLOW WITH THE FIST. BERG, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:317, 1927.

A small tear of the parietal peritoneum on the right side close to the ascending colon, a tear completely separating the right kidney into an upper and a lower portion and a tear through the front wall of the inferior vena cava large enough to admit the tip of a finger resulted from a blow a husband gave his wife. The tear of the vein was explained by a violent tug occurring when the kidney was split and the cava violently jerked toward the right by the renal vessels. Death from the large retroperitoneal hemorrhage did not take place until fifteen hours after the infliction of trauma.

E. R. LE COUNT.

DEMONSTRATION OF MURDER BY SHOOTING SEVEN YEARS AFTER ITS COMMISSION. DRYENFURTH and WEIMANN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:319, 1927.

Roentgenologic examination of the body, mainly of the skeleton, disclosed a bullet close to the first cervical vertebra. Its entrance was a small wound at the back of the neck, thought at the time when it was sustained to be a nail wound received when the deceased fell dying supposedly from acute heart disease. The bullet had grooved the dorsal margin of the foramen magnum. The murderer's wife gave the police their first news of the murder by shooting, and it was subsequently corroborated by other evidence.

E. R. LE COUNT.

THE BLOOD GROUPS AND THEIR APPLICATION IN LAW. F. SCHIFF, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:369, 1927.

The author reviews the developments in blood grouping to the present day. He discusses at some length the applications of blood grouping to law: identification of blood stains and cases of disputed parentage. The three multiple allelomorph hypothesis is upheld as the method of inheritance of the groups. Some attention is given to transfusion, and the relations between blood groups and various pathologic characters.

LAURENCE H. SNYDER.

PRACTICAL EXPERIMENTS WITH THE DETERMINATION OF THE BLOOD GROUP IN STAINS. LEONE LATTES, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **9**:402, 1927.

Summarized histories are given for cases in which the identification of blood stains was undertaken by means of iso-agglutination reactions. The applications of the results to the legal aspects of each case are pointed out. The stains varied from those that were freshly-made to those that had been made for eighteen months.

LAURENCE H. SNYDER.

ISO-AGGLUTINATION AND ITS FORENSIC APPLICATION IN RUSSIA. N. W. POPOFF, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **9**:411, 1927.

Popoff reviews the work on blood grouping that has been carried out in Russia. Starting with the work of Kolzoff, in 1921, on the inheritance of the groups, he lists the various projects, giving a short summary and a complete citation for each. Special attention is given to the legal aspects of blood grouping. Among the phases studied by various Russian workers are the following: the physicochemical basis of agglutination, the production of group-specific rabbit-antisera, differential sedimentation rate in the four groups, the relations of blood groups to various diseases (mental diseases, malaria, tuberculosis, syphilis, etc.), the distribution of the four groups among various peoples (Russians, Jews, White Russians and Ukrainians), the anthropologic significance of blood grouping, the racial index, transfusion in its various aspects, the technic of grouping, auto-agglutination, pseudo-agglutination, the inheritance of the groups, the identification of blood stains by iso-agglutination and the determination of percentage by blood groups. Histories of a series of cases of disputed paternity are given.

LAURENCE H. SNYDER.

BLOOD GROUPS AND CRIME. KURT BÖHMER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **9**:426, 1927.

In a study of the blood groups of 1,034 criminals in Schleswig-Holstein, an abnormally large percentage of group B was found (20 per cent). The cases are variously analyzed according to locality, nature of the crime, length of term and type of criminal.

LAURENCE H. SNYDER.

MICROSCOPIC EXAMINATION OF THE ORGANS OF EXHUMED BODIES. F. SCHWARTZ, *Schweiz. med. Wchnschr.* **56**:996, 1926.

The body of a young woman was exhumed four months after burial. Decomposition was advanced, especially of the skin and muscles. The uterus was enlarged and the internal lining was covered with a dirty material. Microscopic examination showed almost complete loss of nuclear structure, but numerous blue stained, sharply defined spots were noted in many organs, especially in the uterus and the kidney, and these spots were composed of staphylococci. Accordingly, the diagnosis of metrophlebitis and general septicemia with staphylococcal emboli was ventured.

WILLIAM HUEPER.

CLINICAL AND ANATOMIC STUDIES OF ELECTROPATHOLOGIC EFFECTS. J. JELLINEK, *Wien. klin. Wchnschr.* **39**:1206, 1926.

So-called electric burns may be classified as electric current marks or figures, electrotraumatic and electrochemical lesions, electric burns and mixed forms of these types. The electric lesion, which is peculiar, as shown specially by the extensive destruction that may occur in bones, tendons and joints, usually heals aseptically. Surgical procedures are unnecessary and even contraindicated, because the vascular walls are friable in the first two weeks, hence

difficult to ligate, and the full extent of the lesion does not become evident before the third week. In persons who survive the first shock, circulatory symptoms are prominent; subsequent degeneration of the nervous system may prove fatal. Different types of electric death—momentary, retarded, interrupted—are determined by acute edema of the brain and lungs. Sometimes, victims who apparently are dead may be revived by prolonged artificial respiration.

WILLIAM HUEPER.

TWO DEATHS FOLLOWING THE USE OF SANOCRY SIN. O. HELMS, *Ugesk. f. Laeger* **88**:932, 1926.

Two young women, aged 18 and 20, developed angina, fever, exanthem, albuminuria and diarrhea following injections of sanocrysin for therapeutic purposes; death resulted. In one of the patients a severe ulcerative colitis and fatty liver was found, in addition to pulmonary tuberculosis.

Technical

ESTIMATION OF PANCREATIC ENZYMES AND VALUE OF SUCH DETERMINATIONS FROM A CLINICAL STANDPOINT. L. MARTIN, *Arch. Int. Med.* **39**:343, 1927.

Estimations of pancreatic enzyme activity may be of paramount help in making a differential diagnosis in choledocholithiasis and in cancer of the head of the pancreas. The method is briefly as follows: Place 1 cc. of bile in a 19 cc. buffer solution, p_H 7.7, and 1 cc. of a 1:20 mixture in 29 cc. of the same buffer. This makes a 1:600 dilution. Into three Folin-Wu tubes place, respectively, 1 cc. of a 1:20 dilution; 0.1 cc. of 1:20 into 0.9 cc. of standard buffer and 1 cc. of the 1:600 dilution. To each tube add 1 cc. of a 1 per cent solution of starch. Incubate for thirty minutes in a water bath from 38 to 40 C. Then add 2 cc. of alkaline copper sulphate and complete the test as for a blood sugar determination. In normal cases, digestion will be practically complete in tubes 1 and 2. Tube 3 may be the only one in which it will be necessary to make a reading. To arrive at a unit of comparison, multiply the amount found in tube 3 by 100, that in tube 2 by 33.3 and that in tube 1 with a dilution of 1:20 by 3.3.

Standard

————— \times amount of glucose in standard $\times 100 =$ mg. of glucose.
unknown

S. A. LEVINSON.

ROSE BENGAL TEST FOR LIVER FUNCTION. N. N. EPSTEIN, G. D. DELPRAT and WILLIAM J. KERR, *J. A. M. A.* **88**:1619, 1927.

A vein in the cubital fossa is selected, and 10 cc. of a 1 per cent solution of rose bengal in physiologic sodium chloride solution is injected, and the needle washed through slowly with from 5 to 10 cc. of salt solution, which is held ready in a fresh syringe. The needle is left in the vein, and at exactly two minutes after the injection of the dye a sample of blood (10 cc.) is withdrawn from the needle into a clean syringe and discharged into a centrifuge tube containing a few crystals of potassium oxalate. The tube is carefully inverted two or three times. The needle is again washed by slowly injecting from 5 to 10 cc. of the salt solution, which maneuver prevents the clotting of blood in the needle. At eight and sixteen minutes, respectively, from the time of injection, samples of blood are withdrawn and collected in an identical manner. The needle is then withdrawn from the vein in the arm. The patient should be warned that the dye may color the stools red.

As soon as possible after collection, the blood samples are centrifugalized at a speed of 2,000 revolutions per minute for thirty minutes.

Colorimetric Analysis: Five cubic centimeters of the plasma of each of the samples is separately mixed with 10 cc. of physiologic sodium chloride solution. The diluted plasma of the two minute sample is placed in the wedge of the Hellige colorimeter. This is used as the standard against which the eight and sixteen minute diluted samples are read.

Since the two minute sample represents the highest concentration of the dye in any person, following the injection of a fixed amount of the dye into the circulation, it may be regarded as 100 per cent retention, and the colorimetric readings obtained by comparing the eight minute and sixteen minute specimens with it represent direct percentages of dye retained. Before colorimetric readings are made it is necessary to standardize the Hellige colorimeter used and to correct for any inaccuracies present. The colorimeter is standardized by the comparison of one sample of plasma against itself; the reading should be 100.

The colorimetric readings thus obtained indicate the ratio between the first or control sample and the subsequent samples. This obviously indicates the speed with which the dye leaves the circulation.

In normal persons, the eight minute sample is usually 50 per cent, varying from 40 to 60 per cent, and the sixteen minute sample varies from 23 to 30 per cent. These percentages represent the amount of dye retained in the circulation. In acute infections and other pathologic processes of the liver there is marked delay in the passage of rose bengal from the blood. The test is of value in the diagnosis and prognosis of certain diseases of the liver.

A SIMPLE COLOR TEST FOR BROMINE IN BODY FLUIDS. GEO. H. BELOTE, J. A. M. A. **88**:1696, 1927.

Strips of filter paper are soaked in saturated solution of fluorescein in 60 per cent acetic acid. If kept dry such strips can be used at any time. The suspected fluid is placed in a test tube and a few crystals of potassium permanganate are added; after agitation, a few drops of concentrated sulphuric acid are added and the fluorescein paper after it is moistened with 2 per cent acetic acid, is held at the mouth of the tube. The presence of even minute quantities of bromine is indicated at once by a rapid change of the paper from the original yellow to a bright pink. In cases in which bromide intoxication is suspected, this test may be of great value. The reaction is not interfered with by the presence of iodine or chlorine.

THE "ACID TEST" IN GASTRIC AND DUODENAL ULCER. WILLIAM L. PALMER, J. A. M. A. **88**:1778, 1927.

The introduction on an empty stomach and when the patient is free from distress of 200 cc. of 0.5 per cent hydrochloric acid, repeated in thirty minutes and again at the end of the hour, if necessary, usually give rise to typical distress in the presence of ulcer.

SUGAR AND CHLORIDE CONTENT OF ARACHNOID FLUID DURING ANTIMENINGOCOCCUS SERUM TREATMENT. JOHN P. CAFFEY, STAFFORD McLEAN and RUTH C. SULLIVAN, J. A. M. A. **88**:1859, 1927.

In acute purulent meningococcus meningitis before treatment, the sugar concentration of the cerebrospinal fluid was markedly decreased in 90 per cent of the cases. A small number of cases showed normal sugar concentration.

The administration of specific serum in children older than 6 months who recovered caused an increase in the cerebrospinal fluid sugar to normal within from seventy-two to ninety-six hours.

The administration of specific serum in patients younger than 6 months who recovered caused a slower increase in cerebrospinal fluid sugar. Normal values were not reached during two weeks after the beginning of treatment.

The administration of specific serum in uncomplicated fatal cases did not cause a material increase in cerebrospinal fluid sugar.

The cerebrospinal fluid chloride content was reduced in 60 per cent of the cases before treatment. In cases in which the chlorides were decreased, the administration of serum caused an increase to normal in cases in which there was recovery.

AUTHORS' SUMMARY.

DO TUBERCLE BACILLI PASS THROUGH THE NORMAL KIDNEY? WILLIAM M. SPITZER and WILLIAM W. WILLIAMS, J. A. M. A. **88**:1870, 1927.

Tubercle bacilli appear in the urine only when tuberculous lesions exist in either the urinary or the genital tract.

DETECTION AND INCIDENCE OF HUMAN INTESTINAL PROTOZOA BY THE SIGMOIDOSCOPE. MOSES PAULSON and JUSTIN M. ANDREWS, J. A. M. A. **88**:1876, 1927.

The results show that the sigmoidoscope is of distinct value in obtaining specimens of feces for parasitologic examination.

TUBERCLE BACILLI IN THE GASTRIC CONTENTS OF CHILDREN WITH PULMONARY TUBERCULOSIS. P. F. ARMAND-DELILLE and J. VIBERT, Presse méd. **35**:402, 1927.

The following method is suggested as of value in the diagnosis of pulmonary tuberculosis in children, because, as a rule, sputum cannot be obtained in such cases. From 80 to 100 cc. of tepid boiled water is introduced in the child's stomach as soon as it awakes in the morning. The aspirated water contains bronchial secretions that have been swallowed. The fluid is centrifugalized and the sediment stained for tubercle bacilli. Tubercle bacilli were found by this method in 30.9 per cent of the 174 gastric contents. In thirteen of the positive cases, the presence of the bacilli confirmed the physical and the roentgenologic signs; in eighteen cases, the only other indications of the diseases were the roentgenologic signs; in three cases, physical and roentgenologic signs were both absent.

ANIMAL AND CULTURAL TESTS FOR THE DEMONSTRATION OF TUBERCLE BACILLI IN SPUTUM. F. SCHMIDT, Centralbl. f. Bakt. **101**:364, 1927.

Forty sputums, negative microscopically for *B. tuberculosis*, were tested with sulphuric acid and cultivated on potato medium and egg medium and injected into guinea-pigs. In eleven cases, the guinea-pigs reacted positively, with six positive reactions for the egg medium and five for the potato medium. Injection of culture of the sputum in guinea-pigs is the safest way of diagnosing tuberculosis.

PAUL R. CANNON.

TECHNIC AND SIGNIFICANCE OF NITRITE TEST IN URINE. R. HIRSCH, Deutsche med. Wchnschr. **53**:489, 1927.

Fresh urine is mixed with an equal volume of Gries' reagent, consisting of 0.2 Gm. of alphanaphthylamine dissolved in 20 cc. of boiling water and filtered into 150 cc. of diluted acetic acid. This solution is mixed with a solution of 0.5 Gm. of sulphanilic acid in 150 cc. of diluted acetic acid. The mixture is stable in a dark bottle. A red color indicates the presence of nitrites. A negative reaction means either that the urine is sterile, or that it

is infected with bacteria which do not form nitrites (gonococci, streptococci or tubercle bacilli). Two further possibilities are that not enough nitrites have been formed or that the urine did not contain enough nitrates. These last two possibilities are checked in the following manner: A two hour incubation at 37 C. gives the bacteria time to produce enough nitrites. Another sample of urine is incubated for one-half hour after the addition of a few drops of a 10 per cent solution of sodium nitrate, and is then tested for nitrites. A positive nitrite reaction in an acid urine makes infection with the colon bacillus highly probable. Any positive result is reliable; negative results do not exclude infection.

A METHOD FOR COLLECTING THE BLOOD FROM THE SUPRARENAL GLAND IN THE DOG, WITHOUT FASTENING, NARCOTIZING, LAPAROTOMY OR PROVOKING ANY PAIN. Y. SATAKE, T. SUGAWARA and M. WATANABÉ, *Tohoku J. Exper. Med* 8:501, 1927.

Blood was collected directly from the cannulated lumbosuprarenal vein following desensitization of the region by the bilateral extradural section of the dorsal roots of the ninth thoracic to the third lumbar nerves. Blood collected from a quiet dog by this method and tested on a segment of the intestine of a rabbit had a mean concentration of epinephrine of 0.0001 mg. per one cubic centimeter of blood. This low concentration is in contrast to the determinations made on blood collected by the cava pocket method in either the nonanesthetized deafferented dogs or the anesthetized normal dogs, although the exaggeration due to the preparation of the pocket could be reduced by deep anesthesia.

E. B. PERRY.

KAHN'S SYPHILIS TEST. L. NIEUWEJAAR, *Acta. path. et microbiol. Scandinav.* 3:534, 1926.

Kahn's test is much simpler and can be carried out more rapidly than the Wassermann test, and it requires a much smaller equipment. The reading of the results is possibly somewhat more difficult than with the Wassermann reaction and is more dependent on subjective judgment. Kahn's test seems to be a reliable aid to serodiagnosis of syphilitic conditions, and in the preponderating majority of cases (about 90 per cent) it gives in the author's material the same result as the Wassermann test. The divergent results are mostly reactions lying on the border line, which are difficult to judge. They seem, however, to show that with Kahn's test there is less sensitivity in some cases of treated primary and secondary syphilis than with the Wassermann test. On the other hand, the divergent results in the tertiary forms go distinctly in favor of Kahn's reaction, while in case of congenital and latent syphilis the one test seems to have no advantage over the other. Kahn's test supplements the Wassermann test in an excellent manner, and the question is whether the new test could not also be employed alone, without constant control with the Wassermann test. In case of hospitals, smaller laboratories, etc., where the necessary equipment for the Wassermann test is lacking this question has some importance, and the results hitherto attained are so good that there is every reason for trying the method further.

AUTHOR'S SUMMARY.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, May 12, 1927

EUGENE L. OPIE, *Presiding*

DERMOID CYST OF KIDNEY. MOSES BEHREND.

The specimen was taken from a white woman, aged 35, whose chief complaint was abdominal pain. The past history was unimportant except for the fact that the patient had had attacks of indigestion for the past ten years. Twelve weeks before presentation, she was suddenly seized with pain in the right hypochondriac region, associated with vomiting and jaundice. This was followed by other attacks at intervals without jaundice. In addition to these symptoms there was an easily palpable mass in the left hypochondriac region. This extended several inches below the costal border, especially on deep inspiration. Many thought it might be an enlarged spleen, but the cytoscope and the roentgen ray revealed the fact that this was a tumor of the kidney and not of the spleen.

An incision was made in the left rectus. The mass was easily found after incising the peritoneum and was connected with the lower pole of the kidney. The kidney with the cyst was removed. The ureter was much atrophied. On incision of the tumor, the wall was found to be hard and calcareous; within was a whitish, mucilaginous material resembling that seen in dermoid cysts elsewhere. Curiously enough, a small dermoid cyst of the left ovary was also removed at the same time. Gallstones were also found, but an operation was not performed on the gallbladder.

"WEeping UMBILICUS" PERSISTENT DOUBLE URACHUS. MOSES BEHREND.

The patient was a white girl, aged 16, whose chief complaint was moisture around the umbilicus. About two and one-half years before presentation, the patient began to have a thick, odorous discharge containing pus from the umbilicus. It was always worse around the time of menstruation. Recently pain and itching had been associated. The umbilicus was circumscribed under gas anesthesia, and the incision was continued deeply until the urachus was reached. A few centimeters from the umbilicus, the urachus branched and continued in this way to the fundus of the bladder. The urachus was then excised, and the ends that remained attached to the bladder were cauterized with the electric cautery.

In the classic book of Cullen on the umbilicus, no mention is made of a double urachus found at operation.

A CASE OF ACUTE PNEUMOCOCCUS AORTIC ENDOCARDITIS WITH PERFORATION OF THE VENTRICULAR SEPTUM. CHARLES-FRANCIS LONG.

On March 5, 1927, a white man, a textile worker, aged 48, was admitted to the tuberculosis service of Dr. Edward Weiss at the Philadelphia General Hospital. For three weeks, respiration had caused him pain in the right thorax and there had been a productive cough with whitish expectoration until forty-eight hours before admission, when he "felt something burst in his chest," and he had a profuse hemoptysis. There was a long history of overindulgence in alcohol and tobacco; but there was no history of contact with tuberculous patients, and no member of the family had had the disease. The patient had never been seriously ill. The patient was pale, thin, perspired moderately and looked

sick. There were signs of consolidation of the upper and middle lobes of the right lung with congestion at the right base, a temperature of 104 F. a respiration rate of 30 and a pulse rate of 100. The only abnormal cardiac condition was a systolic murmur at the aortic area. The Wassermann reaction was negative. There was moderate anemia and a leukocytosis of 16,800 with 91 per cent polymorphonuclear cells. Tubercle bacilli were found in the septum in the second of four consecutive examinations.

Two days after the examination, he became delirious and continued so until death three weeks later. The fever declined by lysis with a flareup to 102 F. five days before death. The pneumonic consolidation of the right upper lobe never resolved, and the cardiac condition did not change until the preagonal hours, when failure set in.

At autopsy the condition was diagnosed as pulmonary tuberculosis and lobar pneumonia, probably of tuberculous etiology. The lungs showed old healed tuberculous scars at both apexes, with a small, almost obliterated cavity in the left, a thickened pleura over the right lower lobe and a fresh fibrinous pleurisy at the left base. The right upper lobe was the site of an unresolved pneumonia, not caseous. The right middle and lower lobes and the left lower lobe were congested, but not consolidated. The microscope revealed an organizing fibrinous pneumonia. The heart, weighing 450 Gm. was firm and fleshy; the pericardium was normal and the muscle a little edematous. Attached to the anterior aortic leaflet on its ventricular aspect was a yellowish white, firm, cauliflower vegetation measuring 20 by 15 mm. extending down to and attached to the ventricular wall. The other aortic leaflets were normal. The right auricle and ventricle were dilated. Above the posterior leaflet of the tricuspid valve was a small vegetation which proved to be a direct extension from those on the aortic valve. The infection had eroded the interventricular septum at this point and spread through to the wall of the right auricle. Smears taken from the vegetations were filled with gram-positive diplococci, presumably pneumococci.

In a study of 835 fatal cases of pneumonia, Locke found 30 cases of acute endocarditis, but in only 14 was the pneumococcus recovered from the vegetations. On this basis, the incidence of pneumococcic endocarditis in pneumonia is 1.7 per cent. The aortic valve was affected in 40 per cent of Preble's 141 cases of pneumococcic endocarditis.

It is not unusual to find vegetations arising on the margins of a chronic septal defect, but to find an acute inflammatory process destroying the substance of the interventricular septum is rare. This sequence of events is proved in the present case, because the perforation lies above the tricuspid valve, and is surrounded by an area of fresh hemorrhage. With such vegetations in the path of the blood current, embolism and infarction were to be expected, and a fairly large area was found so affected at the upper pole of the right kidney.

The interesting features of this case and specimen can be briefly summarized: 1. The patient died of pneumococcic pneumonia though he had bilateral apical tuberculosis and a positive sputum. 2. The heart was the site of a pneumococcic endocarditis with a perforation of the ventricular septum.

A CASE OF PERITONEAL CYSTADENOMA. JOSEPH MCFARLAND and JOHN L. ATLEE, JR.

This interesting specimen was removed from the abdomen of a white married woman, aged 31. She had three children, the last of whom was born eighteen months prior to presentation. Except for the fact that this last child presented by the breech, there was nothing unusual about the parturition. The patient's recovery was uneventful, except that, according to her own statement, her abdomen seemed to have increased to a greater size than usual during the last pregnancy, and to have remained larger than usual after delivery. Almost

ever since the baby was born she had been subject to frequent attacks of epigastric pain, gaseous eructations, and diarrhea with the passage of yellowish stools. The attacks occurred about once a month and seemed to weaken her. She had lost about 10 pounds (4.5 Kg.) in weight. The only other important event in the patient's history was an attack of what was regarded as appendicitis, about four years previously, from which she recovered without operation.

Physical examination of the patient showed her abdomen to be much distended with fluid, and to contain a large, fixed, nodular, doughy mass in the epigastrium, and numerous similar but smaller masses elsewhere throughout the abdomen. There was no tenderness or muscular rigidity.

An exploratory laparotomy was performed, and through the median incision about 4,000 cc. of slightly turbid, amber-colored fluid of about the consistency of thin molasses escaped, together with several thin-walled, elastic, translucent spheres, one of which fell on the floor and rebounded like a rubber ball. The abdominal cavity was found to contain much more of the mucilaginous fluid and quantities of the cysts, varying in size from several centimeters in diameter to infinitesimal proportions, and either hanging together by slender pedicles, sessile or amalgamated into a general spongy mass. Such a tumor mass was found either springing from the omentum or attached to it, and similar masses occurred elsewhere, the second largest being near the vermiform appendix.

Attempts to discover the source and origin of the tumor and of the cysts failed, as those organs that could be examined, including the uterus and ovaries, seemed to be normal, except that two small pedunculated cysts were attached to the posterior wall of the uterus. The vermiform appendix could not be found without the removal of a mass of adhesions and cysts that it was deemed unwise to disturb.

As much of the spongy tumor tissue and as many of the cysts, both large and small, especially those attached by pedicles as was easily accessible, were removed, the abdominal cavity emptied as far as possible of its collection of mucilaginous fluid, and the wound closed.

The patient recovered from the operation, and the wound healed without complications. Since this tentative treatment, she has been receiving roentgen-ray treatment, and has now been without symptoms for four months; there is not palpable tumor, and fluid has not accumulated.

To the naked eye, the general appearance of the cysts, especially those that lay free in the abdominal cavity, immediately suggested either hydatid disease or mole of the bladder. It was easy to differentiate between them. The resemblance to echinococcus cysts disappeared when careful scrutiny revealed yellowish viscid contents instead of the limpid watery fluid of the hydatids, and the thin walls were tough and elastic rather than brittle and laminated. Moreover, there were no cysts within cysts and no hooklets.

The differentiation from the hydatidiform mole was easily made with the aid of the microscope, for each cyst was found to consist of a thin layer of fibrillar connective tissue, scarcely having a cellular endothelial covering on the outside so scattered were the cells, but lined with the vestiges of what once had been a columnar epithelium on the inside—the cells separated, partly desquamated, more or less spindle-shaped, and eosinophilic—evidently the source of the mucous contents. Such structure is different from the cystically swollen chorionic villi covered by the cells of Langhans on the outside, characteristic of the "bladder mole."

Chemical examination of the contents of the cysts made by Dr. George Robson, showed that they gave all of the mucin reactions and that they yielded traces of sugar on hydrolysis with the appropriate reagents.

Definite information of the true nature of the lesion is not available, and as the patient seems to be on the way to recovery rather than death, may never be. Several theories, however, should be entertained as probable explanations.

The first explanation suggests origin from a diseased vermiform appendix. It will be remembered that four years previously the patient suffered from what was supposed to be an attack of appendicitis, and that at the time of the operation the appendix could not be examined because of the extent of the disease in its area.

The second explanation is that at one time there was a small ovarian cystoma that ruptured into the abdominal cavity, scattering its cells from which the neoplasm grew as the traumatism in the ovarian tissue repaired and perhaps cured the original lesion.

It was also suggested that the condition might have resulted from the admission of chorionic villi, from the embedding ovum, into the abdominal cavity, by way of the fallopian tubes, but there was no evidence of chorionic structure about the cysts; so the theory need not be further considered.

THE PATHOGENESIS OF TETANY. L. E. HOLT, JR.

Alkalosis is present in certain varieties of tetany, but it has not been clear whether the alkalosis itself caused tetany, or whether it acted indirectly by lowering the calcium ion activity. An attempt was made to answer this question by producing an alkalosis under conditions such that a lowering of the calcium ion activity could not be supposed to take place. Mixtures of sodium hydroxide and calcium hydroxide injected into dogs produced a marked alkalosis and a great elevation of the blood calcium, but did not produce tetany. Tetany accompanied by an alkalosis was produced by injections of sodium bicarbonate and cured by subsequent injections of the mixture of sodium hydroxide and calcium hydroxide in spite of the fact that the alkalosis was further increased by the injections of alkali. This seemed to indicate that alkalosis itself was not a case of tetany.

In order to ascertain if sodium bicarbonate tetany could be due to sodium poisoning, observations on the blood sodium were carried out. Injections of a solution of 1.3 per cent sodium bicarbonate, having approximately the same sodium content as blood serum, would eventually produce tetany, although the blood sodium was not elevated. Injections of hypertonic sodium chloride, on the other hand, raised the blood sodium to high levels without producing tetany. This seemed to indicate that bicarbonate tetany could not be attributed to sodium poisoning.

It was found that dogs with hypercalcemia produced by parathyroid extract were definitely refractory to the production of sodium bicarbonate tetany. Furthermore, sodium bicarbonate would not produce tetany if an alkaline solution of calcium were injected simultaneously. The preventive effect of calcium on bicarbonate tetany suggests that this form of tetany is due to a reduction of the calcium ion activity, even though the stoichiometric calcium is not markedly lowered.

(This work was done in collaboration with Drs. R. J. Striegel, W. A. Perlzweig, and C. F. Harris of the Departments of Pediatrics and Medicine, Johns Hopkins University, Baltimore.)

Book Reviews

BIOGRAPHICAL SKETCHES AND LETTERS OF T. MITCHELL PRUDDEN, M.D. By LILLIAN E. PRUDDEN, Cloth. Price, \$3. Pp. 311. New Haven: Yale University Press, 1927.

The lives of physicians are rarely of any great interest to the public. Occasionally physicians whose work is in public health or some phase of medicine, such as tuberculosis, which touches a large group of people, may have contacts sufficiently dramatic to render them worth recording. Miss Lillian E. Prudden has given an attractive portrayal of her brother—his early struggles and final achievement.

Prudden's scientific life was coterminous with the great Renaissance in scientific medicine which, beginning with the fundamental discoveries of Pasteur and Koch in bacteriology, turned the whole science of medicine into new lines, and which has not even yet spent its force. In those days any one with a moderate amount of technic and some industry could attach his name to a new bacillus, and after the discovery of diphtheria antitoxin, it was felt that all the infectious diseases would shortly be under control. Every one knows how little this optimism has been justified by the results, but the period was one of extraordinary intellectual exaltation. Prudden was in it in one sense, and not in it in another. He had a mind of unusual crispness from the intellectual point of view—almost mathematical in its clarity, in the segregation of its compartments and interests. Probably some of this was due to his close relationship to Francis Delafield, who had a mind of marked limitations in every direction except that of morphologic pathology and its application to medicine. This influence made Prudden extremely critical, perhaps quite properly so, of all hasty work and vague conclusions. It limited his own production and that of his pupils, a matter on which the world may perhaps be congratulated, when the present eruption of badly written records of hastily conducted experiments and sloppily drawn conclusions is considered.

Prudden did some bacteriologic work of an excellent sort, notably his paper on the lesions produced by dead tubercle bacilli, but his interests were far more in the practical application of his bacteriologic knowledge to public health. It was indeed in this line of public health that his chief work was accomplished. Unfortunately for his personal glory, it was all done through recognized public health agencies, and while the results, as shown by the extraordinary development of the New York City Board of Health and its laboratories, were admirable for the community, Prudden gained little if any credit except among the few who knew his almost daily activities with the affairs of that institution, and later in those of the State Board of Health. While he recognized that the Rockefeller Institute, of which he early became a member of the scientific board, was properly engaged in research for the most part on the general problems of biology, he would have liked to have seen that institution take a much greater practical interest in public health, and often discussed the establishment of a museum of public health, in which methods and results could be demonstrated to the public.

He was an extremely good popular writer, and his two little books on "Dust and Its Dangers," and the "Story of the Bacteria" have done infinite good in schools and households by popularizing knowledge on these subjects. His magnum opus, of course, was the carrying on of the book which Delafield

had originally written in 1872, as a small guide to "Morbid Anatomy," and the development of that work into what many teachers consider the best student text in the English language.

He led another and completely separate existence about which only a few knew anything. For years he spent his summers in the Southwest exploring the cliff dwellings in the desert in company with a couple of guides. The people with whom he worked were immensely fond of Prudden and he of them, and he carried on a long and most amusing correspondence with his acquaintances of the western desert. Selections from the letters are included in this book, but he never spoke in public of his trips, and even those who worked nearest him in the laboratory knew little or nothing about what he was doing during four months of the year. About the first of October Prudden would return, bronzed and cheerful, then develop the bronchitis which he always had following the summer spent in the germ-free atmosphere of the desert, due, of course, to the inhalation of a large number of organisms in the Pullman car coming East and on the dusty streets of New York. After his convalescence he would drop into his work of the winter—always an admirable teacher, clear and patient with the good students, amusingly critical of the poor ones, but always somewhat reserved. The students had an immense respect for him, but he stood apart from them and to a certain extent from his own research workers. He never could descend into the arena intellectually, though he was singularly fond of the amateur boxing matches at the New York Athletic Club, which he religiously (if the phrase may be permitted) attended.

He trained a generation of physicians to see clearly along pathologic lines. He should have trained a generation of surgeons in New York, but they were apparently more interested in learning the names of the various things which they had to cut through during an operation, due largely to the stimulating personality of George Huntington the anatomist. They therefore, much to their own detriment, did not take up pathology and bacteriology in the combined department over which Prudden sat for many years. Surgical work in New York could not be better from the anatomic standpoint than it has been, but it could have been more fertile if the surgeons had known more pathology and bacteriology. It is true that there was about Prudden's laboratory a certain contempt for the vague generalities of the average practitioner with the knife or stethoscope, and a man who came there to spend a week to learn all about tumors was not warmly welcomed, but those who did go there, and were willing to sit down and devote themselves, found ample material to study, and a warm welcome from the "Chief."

It is an interesting life that Miss Prudden records: the New England clergyman and his big family; the strong intellectual honesty which he bequeathed to his son as a characteristic of that Puritan breed; the poverty and difficulties of the laboratory in which Prudden worked during the early days of the "P. and S." before it became a part of Columbia. This laboratory, however, was the first of its type in the country, and Prudden made it what it was to be in later years with the aid of a shrewd practitioner of obstetrics, Dr. James W. McLane, and the constant assistance of Francis Delafield, who helped financially and intellectually at every stage. In later years came ease, travel, trips to the Western desert, the broad opportunities of the Rockefeller Institute, to which he gave all of his time after his retirement from teaching, the rising appreciation of his contributions to the public health agencies of the city and state of New York—all came as his reward. These various stages are laid down by his sister in the well written text illuminated, as occasion suits, by a judicious selection of letters. It is a fine survey of the career of one of America's great medical teachers.

ALLGEMEINE UND EXPERIMENTELLE PATHOLOGIE. Nach Vorlesungen für Studierende und Ärzte. Von DR. HERMANN PFEIFFER o.ö. Professor und Vorstand der Lehrkanzel für allgemeine und experimentelle Pathologie an der Universität Graz. Zweite, vermehrte und verbesserte Auflage. Mit 56 teils mehrfarbigen Abbildungen im Text und 8 mehr-farbigen Tafeln. Price, 22.50 marks. Pp. 649. Berlin: Urban & Schwarzenberg, 1927.

This volume, the author tells us, was designed to serve as an introductory course in pathology to undergraduate students in medicine. The author has avoided the introduction of all technical matters and has attempted to present the subject of general pathology in a lucid manner for the beginner. There are several publications on pathologic physiology, notably that by Krehl and that by Loewit, which discuss in detail the theory of disease and the disturbance of normal functions in the individual organs. In the present volume, the author gives a careful review of what is known concerning the manner of development of disease processes, and discusses the most important bodily systems in which disturbance of function leads to clinical manifestations of disease.

The volume is divided into eleven chapters of varying length, and of these, the first three chapters are devoted to a discussion of the determination of a disease process and to the important factors bringing about functional disturbances. Starvation and dietary deficiencies are dealt with, illustrated by examples taken from experimental work. Physical, chemical and parasitic causes of disease are discussed in some detail, but within the compass of a volume of this nature, none of the factors is given detailed attention. The author even enumerates the many bacteria which are the cause of human illness, and the comment made is sufficient only to give superficial information. One is much disappointed in the limited number of references that accompany each chapter; furthermore, the most recent references are not always noted. There is an unusual paucity of references to articles written in the English language.

The chapters on inflammation and on fever are rather well written for a simple text. Throughout the book, one is struck, however, with the fact that the author is bringing his discussions down to the level of the simple reader who may not have a subsequent interest in biologic studies.

The remaining chapters deal with the changes in the state of the blood and its influence on the constitution, the diseases arising from disturbances in the circulation, the disturbances of the respiratory system, metabolic disturbances and disturbances of internal secretion. There is a general discussion on the formation of tumor.

The book contains much superficial information concerning the process of disease. It is of little value to the instructor in medicine, the practitioner or the advanced student. The book deserves a place in the library of the undergraduate student who, after completing his primary years in the laboratory, desires to review the application of pathologic processes to clinical medicine. As the book has been written in fluent language, it is easy to read, and it arouses interest in topics which are only partially discussed.

BONE SARCOMA. By ANATOL KOLODNY, PH.D., M.D., Department of Surgery, University of Iowa. Price, bound, \$5. Pp. 214. Chicago: The Surgical Publishing Company, 1927.

This reprint from *Surgery, Gynecology and Obstetrics* (44:1, 1927), is essentially an atlas with 29 entire pages of illustrations and 108 pages, about one half of which are devoted to illustrations, reproduced photographs of gross and minute structure of tumors of the Registry of Bone Sarcoma of the American

College of Surgeons, which "authorized" the publication of the book. There is no index or bibliography. It is apparently the writer's interpretation of the material from 700 cases in the so-called "Codman Collection." The account written about the illustrations is full of repetition, of which the following from page 44 is an example: "It would be erroneous to attempt to give a typical picture of an osteogenic sarcoma. The large majority of osteogenic sarcomata are histologically atypical, or better still, there is no one type of osteogenic sarcoma. Osteogenic sarcoma is a tumor" (etc.).

This term, "osteogenic sarcoma," introduced by Ewing, is equivalent to the more appropriate "osteoblastoma." The entire work is laudatory of Ewing, with twenty-eight pages devoted to "Ewing's sarcoma," forty or possibly fifty examples of this disease being included in the Registry. "The knowledge of this entity," Kolodny states, "scarce as it is, is unfortunately limited only to those who have studied the Registry material."

The ancient difficulty of estimating the benignancy of giant cell sarcoma receives no aid from this study, as the following indicates (p. 212). "That giant cell tumor is essentially a benign lesion is generally conceded. It is benign in the oncological sense of the word although clinically it may offer serious surgical problems. The question as it stands today is whether or not a giant cell tumor is *always* benign. From the evidence at hand this question is to be answered in the negative. Giant cell tumor is essentially a benign condition and there is no one case on record in which histologically a typical giant cell tumor gave pulmonary metastases of typical giant cell structure. In the few cases recorded in the literature following pulmonary metastases of a giant cell tumor, either both the primary lesion and the pulmonary metastases showed a typical giant cell tumor structure, or the primary lesion" (ste).

It is unfortunate that the efforts resulting in the Codman Collection of records of tumors and of other diseases of the bone have yielded a review as plethoric with careless statement.

The reproduced roentgenograms will undoubtedly meet with prompt application to daily problems. These illustrations of the gross appearances of tumors are the chief merit of the work. A truly enlightening study and advance in the understanding of tumors of the bone should include information obtained by thorough examination after death of the bodies of patients afflicted with such growths. Information of this character is evidently not abundant in the records of the Registry. Failure to appreciate the limitations of evidence furnished by a study of tissues removed during life and of other wholly clinical examinations is once more clearly displayed.

HISTORY OF CARDIOLOGY. By LOUIS FAUGERES BISHOP, M.D., and JOHN NEILSON, JR., M.D., with an Introduction by VICTOR ROBINSON, M.D. Price, \$5. Pp. 71. New York: Medical Life Publishing Co., 1927.

This book is a collection of more or less disconnected paragraphs, a compilation in fact, showing what various writers from the earliest times down to the present have said concerning heart disease. Hippocrates, Galen, Vesalius, Fabricius, Harvey, Morgagni, Senac, Auenbrugger, Corvisart, Laennec, Withering, Stokes any many others are mentioned. A few lines are devoted to each describing, usually accurately and clearly, his contribution to the subject. When one considers that of the seventy-one numbered pages, twelve are devoted to illustrations and eighteen are blank, one sees that the treatment is brief indeed. One may question the good judgment shown in devoting so much space to Schott and Groedel and the Nauheim treatment. One may also

question the good taste of referring, even though with seeming modesty, to the fact that the senior author "in a small way" has taken part in the development of cardiology, especially as in the preface it is stated that "for obvious reasons living cardiologists have not been included in this essay." It does not seem quite proper to refer to the author's frequent visits to Nauheim in order to improve his knowledge of the subject; nor is it necessary to discuss present day methods of treatment. One turns the last page rather expecting to find the business address and the office hours of the authors.

As a reference book for a few outstanding facts in the history of cardiology the book may have a certain use; as a scientific, comprehensive, philosophic discussion of the subject it is not to be recommended.

EVOLUTION OF PREVENTIVE MEDICINE. SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P., Formerly Principal Medical Officer of the Local Government Board of England, and Lecturer on Public Health Administration, School of Hygiene and Public Health, The Johns Hopkins University. Price, \$3. Pp. 256, with 6 illustrations. Baltimore: The Williams & Wilkins Company, 1927.

This book gives only a fragmentary account of the evolution of preventive medicine. It deals for the most part with British phases of this evolution. The presentation is rather sketchy, episodic rather than consecutive and continuous, and it is obvious that sufficient care was not taken with the writing. Thus the hippocratic dictum that "Life is short and Art is long; the Occasion fleeting, Experience fallacious, and Judgment difficult" is ascribed to Plato (p. 13). Roentgen is misspelled Rontgen at least twice; Hopstick is used for Hopstock, Nicolauer for Nicolaier. On p. 215 one reads that temporary immunity results from "inoculation with dead cultures of the respective bacilli in typhoid fevers, in diphtheria, and possibly in scarlet fever"; further, that (p. 216) "immunity from hog cholera is conferred by injecting into susceptible animals the filtrate of the specific organisms." The chapters on sanitation and social improvement, on progress in the eighteenth and early part of the nineteenth century, on poverty and preventive medicine, on the prevention of "fever" including cholera and on disinfection in preventive medicine, are the most interesting because they bring out the work of great English pioneers, of which but little is known generally.

DIE SERODIAGNOSE DER TUBERKULOSE. VON MAX PINNER, Director des Laboratoriums der Städtischen Tuberkulose-Heilstätte Detroit, Northville, Mich. Price, 5 marks. Pp. 88. Leipzig: Johan Ambrosius Barth, 1927.

This booklet is supplement twenty-eight to "Zeitschrift für Tuberkulose." It describes systematically and thoroughly the various methods that may be used in serum diagnosis of tuberculosis, without attempting to decide in any way which is the best or most reliable method in any given category. The large amount of information presented in readily accessible form makes the booklet a trustworthy and time-saving guide in its special field.

Books Received

THE EXPERIMENTAL STUDY OF RAT-BITE FEVER IN RABBITS. By Masakoto Abe. Pp. 165. Japan: Instit. Dermatosyphil., University of Kyoto, 1927.

PHYSIOLOGIE NORMALE ET PATHOLOGIQUE DU GLOBULIN [BLOOD PLATELETS]. By Jacques Roskam. Pp. 151. Paris: Les Presses Universitaires de France, 1927.

MANUAL OF VETERINARY BACTERIOLOGY. By Raymond A. Kelser, Captain, Veterinary Corps U. S. Army, etc. Price, \$5.50. Pp. 500, 92 illustrations. Baltimore: Williams & Wilkins Company, 1927.

L'INFECTION MICROBIENNE ET L'IMMUNITÉ CHEZ LA MITE DES ABEILLES GALLERIA MELLONELLA. By S. Metalnikov. Pp. 139. Paris: Masson & Cie, 1927.

THE HISTORY OF PLAGUE IN AUSTRALIA 1900-1925. By J. H. L. Cumpston, Director-General of Health and Director of Quarantine, and F. McCallum, Quarantine Officer, Commonwealth Department of Health. Issued under the Authority of The Minister For Health. Pp. 238. Melbourne: H. J. Green, Government Printer, 1926.

DIE BIOLOGIE DER PERSON. Ein Handbuch der allgemeinen und speziellen Konstitutionslehre unter Mitarbeit zahlreicher Fachmänner herausgegeben. Von Prof. Dr. Th. Brugsch und Prof. Dr. F. H. Lewy. Vol. 2 (Lieferung 7). Pp. 221-424. Als Einzellieferung nicht käuflich (single leaflets cannot be bought). Berlin and Vienna: Urban & Schwarzenberg, 1927.

SCIENTIFIC REPORTS FROM THE GOVERNMENT INSTITUTE FOR INFECTIOUS DISEASES, TOKYO IMPERIAL UNIVERSITY. Director, Professor Matro Nagayo. For 1926. Vol. 5. Edited by Dr. Yonejimiya-gaw. Tokyo: Shirokane-Daimachi, Shibaku, 1927.

BEITRÄGE ZUR KENNTNIS DER MONGOLOIDEN MISSBILDUNG (MONGOLISMUS) AUF GRUND KLINISCHER, STATISTISCHER UND ANATOMISCHER UNTERSUCHUNGEN (DIE BEDEUTUNG DER GEBÄRMUTTERSCHLEIMHAUT UND DES AMNIONS FÜR DIE ÄTIOLOGIE UND PATHOGENESE DIESER MISSBILDUNG). Von Dr. W. M. van der Scheer. Price, 12 Marks. Pp. 162, mit 44 Abbildungen im Text. Berlin: S. Karger, 1927.

PRACTICAL BACTERIOLOGY, BLOOD WORK AND ANIMAL PARASITOLOGY, including Bacteriological Keys, Zoological Tables and Explanatory Clinical Notes. A Compendium for Internists. By E. R. Stitt, A.B., Ph.G., M.D., Sc.D., LL.D. Rear Admiral, Medical Corps, and Surgeon General, U. S. Navy, etc. Ed. 8, revised and enlarged with 1 plate and 211 other illustrations, containing 683 figures. Price, \$6. Pp. 837. Philadelphia: P. Blakiston's Son & Co., 1927.

MANUALE ATLANTE DI TECNICA DELLE AUTOPSIE. By Professor Enrico Emilio Franco. Messina: Casa Editrice Giuseppe Principato, 1926.

L'ANGINE DE POITRINE ET L'ANGINE ABDOMINALE. By D. Daniéopolu, professor de clinique médicale à la Faculté de médecine de Bucarest, Directeur de L'Institut clinico-médical B de L'Hôpital Filantropia. Price, 140 francs. Pp. 442, 159 figures. Paris: Masson & Cie, 1927.

THE ANTISTERILITY VITAMINE—FAT SOLUBLE E. By Herbert McLean Evans and George O. Burr, with the assistance of Theodore L. Althausen. Memoirs of the University of California. Vol. 8. Price, \$5. Pp. 176, 12 plates. Berkeley, Calif.: University of California Press, 1927.